Changes in gait variability and balance control during exertional walking in adults with chronic obstructive pulmonary disease

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Statements and declarations

Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

David Carter

Authority of access

Statement of contribution to the thesis

This thesis comprises a research investigation that has been completed almost entirely by the candidate, David Carter. The following people also contributed to the work undertaken as part of this thesis:

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  The conception of study design. Attainment of ethics and study registration, participant recruitment, data collection, analysis and interpretation and wrote the first draft of this thesis.

- **Marie-Louise Bird (School of Health Sciences, University of Tasmania, Australia; University of British Columbia, Canada):**

  Study design and attainment of ethics, the overall responsibility of the project, input into the analysis of data and preparation of the thesis.

- **Kiran Ahuja (School of Health Sciences, University of Tasmania, Australia):**

  Study design, ethics application, statistical analysis, interpretation of data, and review of the thesis.

- **Andrew Williams (School of Health Sciences, University of Tasmania, Australia):**

  Study design, ethics application, data collection and analysis, thesis preparation.

- **Robert Talbot (School of Health Sciences, University of Tasmania):**

  Assisted with some data collection

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Statement of ethical conduct

The research associated with this thesis abides by the International and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

The study protocol entitled 'Pilot study investigating changes in balance control during exertional exercise in adults with chronic obstructive pulmonary disease' was approved by the Tasmanian Health and Medical Human Research Ethics Committee;
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The study protocol entitled "Pilot study investigating changes in balance control during walking with exertion in adults with chronic obstructive pulmonary disease" was registered with the Australia New Zealand Clinical Trials Registry;
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Presentations arising from this thesis

Research findings reported in the thesis have been presented at the following meetings:

Changes in balance control during walking with exertion in adults with chronic obstructive pulmonary disease: protocol for a pilot study

- Prepared by: David Carter, Dr Kiran DK Ahuja, Dr Andrew D Williams, Dr Marie-Louise Bird
- Delivered by: Dr Marie-Louise Bird
- Type: Oral presentation
- Abstract attached: (Appendix A)
- Conference: Thoracic Society of Australia and New Zealand -Tasmanian Branch Annual Scientific Conference (2015)

Exertion, Gait regularity and balance in people with COPD: pilot study protocol

- Prepared by: David Carter, Dr Kiran DK Ahuja, Dr Andrew D Williams, Dr Marie-Louise Bird
- Presented by: David Carter
- Type: Poster presentation (Appendix B)
- Conference: Australia New Zealand Falls Prevention Conference (2016)

Changes in balance control during exertional walking assessments in adults with chronic obstructive pulmonary disease

- Prepared by: David Carter, Dr Kiran DK Ahuja, Dr Andrew D Williams, Dr Marie-Louise Bird
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Abbreviations

6MWT	Six-Minute Walk Test
ABC	Activities-specific Balance Confidence
BBS	Berg Balance Scale
COPD	Chronic Obstructive Pulmonary Disease
$ETC0_2$	End Tidal Carbon Dioxide (in mmHg)
FEV_1	Forced Expiratory Volume (in 1 second)
FR	Functional Reach
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart Rate in beats per minute
ISWT	Incremental Shuttle Walk Test
MD	Mean Difference
MMSE	Mini-Mental State Examination
RCT	Randomised Controlled Trial
RPE	Rate of Perceived Exertion
RR	Respiratory Rate (in respirations per minute)
SLS	Single Leg Stance
$Sp0_2$	Peripheral Oxygen Saturation (in mmHg)
TUG	Timed Up and Go Test
UST	Unipodal Stance Test

ABSTRACT

Background

People with Chronic Obstructive Pulmonary Disease (COPD) have high rates of accidental falls. Increased gait variability and poor balance control are known as risk factors for accidental falls in this population. Exertional walking tasks are used in clinical assessments, however changes in gait variability and balance control during exertional walking assessments are not well researched. This study aims to assess changes in gait variability and balance control during and immediately after walking assessments, and the relationship these falls risk factors have with exertion.

Methods

Participants recruited from a pulmonary rehabilitation program performed two Six-Minute Walk Tests (6MWT) and two Incremental Shuttle Walk Tests (ISWT) one week apart, in a randomised order. Gait variability was measured using a gait sensor mat during the walk tests, and balance control was measured using Functional Reach Test (FR) before and after each walking test. The results were compared using a paired t-test. Concurrently, measures of exertion Rate of Perceived Exertion (RPE), Respiratory Rate (RR), Heart Rate (HR), Peripheral Oxygen Saturation (SpO_2), and End-Tidal Carbon Dioxide ($ETCO_2$) were collected during each walking test.

Results

Twenty people (17 females, 3 males), aged 71 (±8) years, with Forced Expiratory Volume in one second (FEV_1) percent 64 (±18%) of predicted, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) rank 2.2 (±0.75) attended on two occasions. There was no statistically significant change in any of the measures of gait variability analysed from start to end-test in either the 6MWT or the ISWT, despite significant statistical change in RPE ($p = .002$, $p = .007$, respectively), HR ($p = .010$, 0.009, respectively), and SpO_2 ($p = .004$, $p = .034$, respectively) for both walk tests, and RR ($p = .006$) in the 6MWT. Stance time standard deviation had a small but statistically significant inverse association with HR (r= - .143, p= .016) in the 6MWT and a positive association with RPE (r= .133, p= .049) in the ISWT. There were no other statistically significant associations with measures of exertion. There was no statistically significant difference in FR between pre or post reach in the 6MWT (30.08 ±6.15, 29.95 ±5.08 cm, respectively; p= .860), or in the ISWT (30.88 ±5.95 pre-test and 30.23 ±5.51cm post-test, p= .463).

Conclusions

There was no increase in gait variability despite participants reaching maximum levels of exertion and balance control, as measured by FR test did not change immediately after participating in the walk tests. These results indicate that participating in the 6MWT and ISWT does not degrade gait variability from baseline levels of exertion in a community-dwelling COPD cohort and supports the continued use of either walking test.

CHAPTER 1

Thesis Overview

CHAPTER 1 Introduction

Chapter one introduces gait variability in Chronic Obstructive Pulmonary Disease (COPD) as a risk factor for accidental falls and describes how gait variability in relation to level of exertion is under researched despite its clinical importance.

CHAPTER 2 Literature review

This chapter reviews the literature relating to the magnitude of accidental falls in COPD, develops the need to determine risk of falling in relation to elevated exertion and provides a rational for using gait variability as an assessment tool for falls risk.

CHAPTER 3 Methods

The Methods chapter contains the pilot study procedure for the study ‘Changes in gait variability and balance control during exertional walking in adults with chronic obstructive pulmonary disease’.

CHAPTER 4 Results

Chapter 4 contains the demographic analysis of the pilot study participants and presents results relating to the study aims.

CHAPTER 5 Discussion

This chapter discusses how the pilot study conducted addresses the study aims, compares findings with current literature, critiques the study protocol and ends with the clinical implications of this research and recommendations for future research in this area.

Introduction

Overview of the problem

Poor gait regularity, reduced balance control, and falls in COPD

Accidental fall rates are high in the COPD population (Beauchamp 2019; Roig et al. 2011) and are associated with poor walking stability (Iwakura et al. 2019; Lahousse et al. 2015; Marques et al. 2017; Yentes et al. 2015; Zago et al. 2018) and poor balance control (Beauchamp et al. 2009; Porto et al. 2015). Unintentional falls are likely to contribute to the large disease burden of COPD and may significantly reduce a person's quality of life (Brooke 2013; Hellstrom et al. 2009). Not only is the probability of falling high in this population, but the likelihood of injury from falls, including bone fracture and bleeding, are magnified by common comorbidities such as osteoporosis, heart disease, anaemia and polypharmacy (Brooke 2013; Lawlor, Patel & Ebrahim 2003a). Pharmaceutical treatment of COPD is non-curative (Vestbo et al. 2013), and listed possible side effects of corticosteroid-type medications (used in the treatment of infective exacerbations of COPD) include muscle weakness, tendon rupture, hypertension and osteoporosis (Warren 2012).

Exercise therapy, delivered as part of pulmonary rehabilitation, has become a mainstay in maintaining physical condition and quality of life in COPD (McCarthy et al. 2015; Vestbo et al. 2013). Exercise tolerance is commonly assessed with exertional walking tasks and best practice management of COPD involves activities in pulmonary rehabilitation at various levels of intensity (McCarthy et al. 2015; Mukundu 2015). Utilising established walking assessments may offer a safe method for determining the impact that maximal or near maximal effort may have on gait variability or balance control. If increased exertion affects balance control during or immediately after walking, this has important clinical implications.

Risk factors for falls in COPD

Researchers have identified common risk factors for accidental falls in the COPD population (Bhosle, Alaparthi & Krishnan 2012; Crisan et al. 2015; Oliveira et al. 2013; Roig et al. 2009). There is a consensus in the literature that people with COPD (compared to age and sex-matched healthy adults) have increased risk factors such as poorer balance, reduced lower limb muscle power, and reduced postural control (Bhosle, Alaparthi & Krishnan 2012; Crisan et al. 2015; Janssens et al. 2014; Oliveira et al. 2013; Roig et al. 2009). Gait impairments are recent additions to the list of validated risk factors specific to fallers with COPD (Lahousse et al. 2015; Yentes et al. 2011). Levels of exertion have not been researched as a risk factor for accidental falls, despite evidence that people with COPD fatigue easily (Boccia et al. 2015) and require a high physiological energy to perform walking tasks (Marquis et al. 2009). Further research is required to describe how risk factors for falling, including postural control and gait variability, are affected by changing levels of exertion.

Gait abnormality and falls in COPD

Gait impairment is prevalent in COPD, is linked to increased risk of falling and reflects disturbance from regular walking patterns across the domains of walking pattern (Lahousse et al. 2015). Specific gait domains impaired in COPD are discussed at length in chapter 2 in the section 'Gait impairment and falls risk in COPD'. Currently there is little evidence available investigating the relationship between gait regularity and exertion levels. Two large population studies have provided a high level of evidence to demonstrate that gait abnormality is associated with increased rates of accidental falls in COPD (Lahousse et al. 2015; Yentes et al. 2011). Additionally, the relationship between falling and gait abnormality becomes stronger as COPD severity increases and gait impairment becomes more pronounced (Lahousse et al. 2015). These findings signpost a relationship between physiological changes in COPD and the control of gait regularity, but the exact mechanism behind these physiological changes is still unclear. While various patterns of oxygen desaturation during exertion have been reported (Ming-Lung, Lin & Shih-Pin 2014), the impact of oxygen desaturation, or increases in carbon-dioxide levels (as markers of exertion) (Chen et al. 2012; Simard, Maltais & LeBlanc 1995) on central control of balance and gait is uncertain.

Balance impairment and falls in COPD

Balance impairment is prevalent in COPD (Beauchamp et al. 2012; De Castro et al. 2016; Jácome et al. 2016) and the interplay between balance systems impaired in COPD is complex (Figure 1.1). Balance impairment is likely related to increased risk of accidental falls (Oliveira et al. 2017; Ozalevli et al. 2011). People with COPD compared to healthy adults score poorly in many of the commonly used measures of balance including the Berg Balance Scale (BBS), Single-Leg Stand time (SLS), and Timed Up and Go test (TUG) (Crisan et al. 2015). The severity of balance impairment correlates with risk of falling and is useful as a predictor of falls (Beauchamp et al. 2009). The exact cause behind balance impairment is not verified in the COPD literature (Boccia et al. 2015), but the effect of fatigue on balance systems is one likely mechanism (Marquis et al. 2009). Balance impairment appears to be moderated by participation in pulmonary rehabilitation (Beauchamp et al. 2010; Mkacher et al. 2015) but it is unsubstantiated if walking with maximal levels of exertion have a negative impact on balance performance. The relationship between exertion and balance impairment is an important area to investigate, as increased exertion levels may place those with COPD at increased risk of falls during exercise testing or participating in activities such as pulmonary rehabilitation.

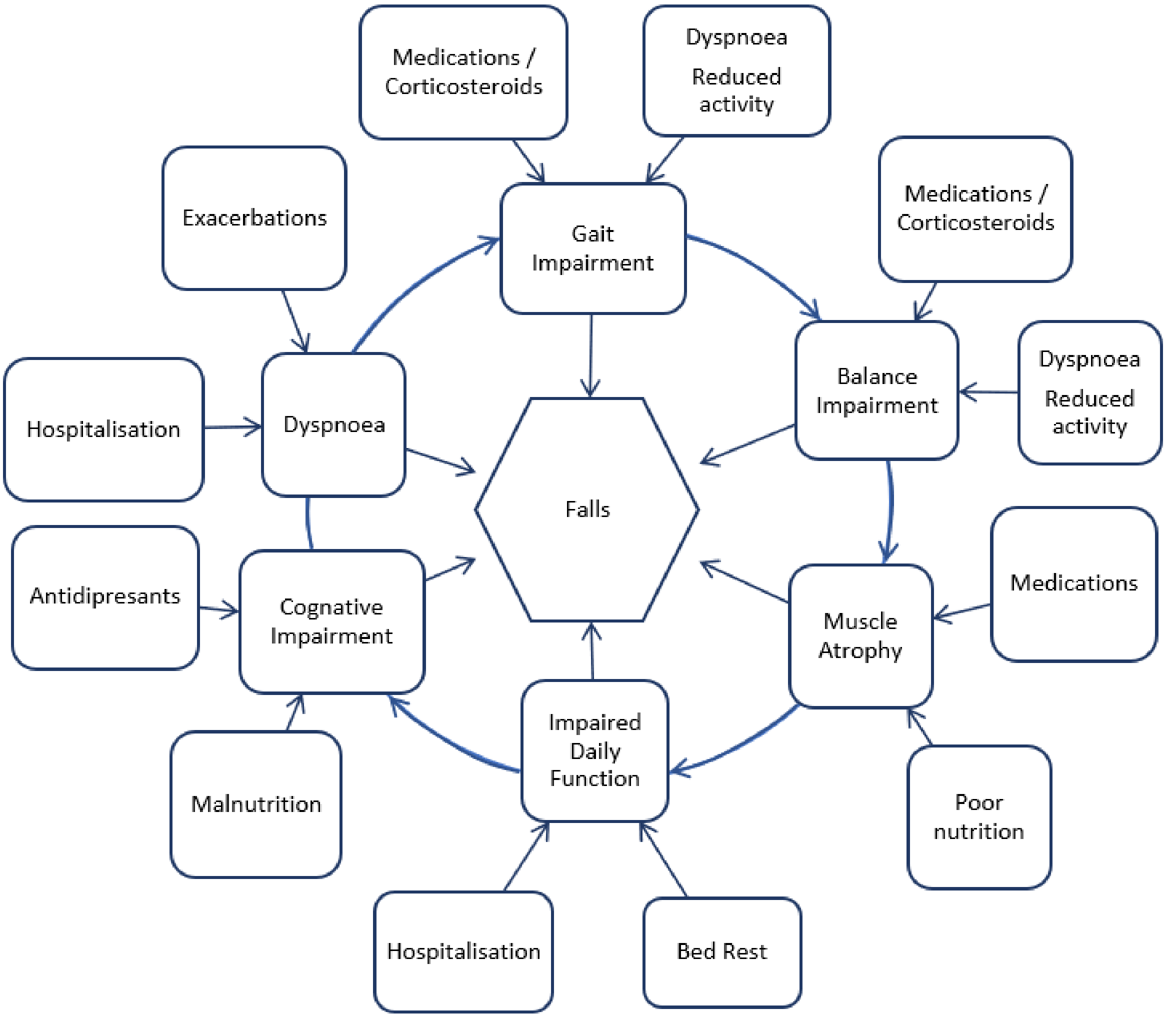


Figure 1.1 Potential interactions of risk factors for falls in people with COPD
Adapted from (Roig et al. 2009)

Significance of Study

Unknown risk of fall with exertion

There is a lack of clinical guidance on safe exertion thresholds for the COPD population regarding falls risk. This deficit in clinical direction remains, despite pulmonary rehabilitation being established as the non-pharmaceutical treatment of choice for managing COPD symptoms. Several systematic reviews of exercise therapy interventions have established pulmonary rehabilitation as beneficial for improving functional balance, dyspnoea, exercise capacity, strength, and walking stability in COPD populations (Jacome et al. 2014; McCarthy et al. 2015; Mukundu 2015). Pulmonary rehabilitation is widely used in the management of COPD, yet few studies investigating safe levels of exertion for participation in exercise therapy have been conducted (Camp et al. 2015). Further study is justified to determine safe levels of exertion to manage a potential increased risk of falling during periods of increased exertional effort.

Research Questions

The primary aim of this study is to determine if people with COPD have increased risk of falling while participating in activities that require elevated or near maximum levels of exertional effort. The study seeks to determine if maximum levels of exertion produce a deterioration in gait regularity during exertional walking tests, and if dynamic balance control reduces directly after exertional testing while measures of exertion remain high. The study is designed to utilise internally-paced as well as externally-paced walking tests to ensure both a self-regulated maximum exertion is achieved and exertion at the voluntary limit is reached.

Hypotheses premise

Because people with COPD have gait impairment and reduced balance control it is possible that increased levels of effortful walking could further compromise walking stability and increase their risk of accidental falls. It is hypothesised that the walking pattern becomes less regular with increased exertion and balance control is reduced immediately after effortful exertion in COPD. A secondary hypothesis is that there is a positive correlation between increasing exertion levels experienced in clinical walking tasks and a decrement in gait regularity and balance control in people with COPD. It is postulated that increased walking exertion will compromise physical systems required to maintain an even walking pattern and reduce dynamic balance control, introducing an increased susceptibility to accidental falls.

CHAPTER 2

Literature review

Literature search method

To inform this literature review a systematic approach and authors topic knowledge was used to search the following online databases between 2015 and 2019:

- Scopus (http://www.scopus.com ,
- Google Scholar (https://scholar.google.com),
- web of science (https://mjl.clarivate.com),
- PubMed (https://www.ncbi.nlm.nih.gov/pubmed), and
- The Cochrane Database (https://www.cochranelibrary.com).

The following keywords and subject headings were used in the search: COPD, Definition, Management, Morbidity, Mortality, Chronic Disease, Osteoporosis, Cognition, COPD exacerbation / acute exacerbation, Walking-test, Six-minute walk test, Incremental shuttle walk test, Falls, Accidental falls, Risk Factors, Gait, Gait impairment / variability, Walking pattern, Balance, Functional balance, Balance assessment/tests, Postural control, Functional Reach, Pulmonary rehabilitation, Quality of life, Exercise, Exertion, Effort. Guidance and published studies identified in the search were limited to articles written in English, published within the last 5 years (unless to describe history or background), and peer reviewed. Articles not included in the literature review were studies that used a qualitative methodology, published in a language other than English, and studies lacking peer review.

Introduction

Overview of this research project

COPD is a chronic lung airflow condition with an undisputed large body of evidence showing it to be one of the leading and increasing global causes of death and disease burden (Mirza et al. 2018; Vogelmeier et al. 2017). The considerable economic and social burden of COPD (Soriano et al. 2017) has prompted substantial research in the area of disease assessment and treatment. Extrapulmonary effects of COPD have been well documented for over two decades now (Agustí et al. 2003) but areas of research focus are probably diversified and diluted by the fact that COPD affects multiple body systems and processes. Despite this, accidental falls and subsequent injury such as fragility fractures are an area of research that overlaps both the older adult population and COPD population and there are multiple systematic reviews identifying validated risk factors of falling which are applicable to both groups (Gillain et al. 2018; Ryrso et al. 2018; Sousa et al. 2017).

Research in the area of falls in COPD was initiated by randomised controlled trials that were commonly limited by small participant numbers, the absence of consensus on outcome measures, and no subcategorising of the COPD population (Beauchamp et al. 2009; Roig et al. 2009). Since then stride-to-stride variations in gait patterns have emerging as a predictive tool for distinguishing between fallers and non-fallers in COPD (Liu et al. 2017; Nantsupawat et al. 2015; Yentes et al. 2015). This research development has probably been enabled by advances in technologies that map spatiotemporal gait patterns such as walking mats and accelerometers. Currently large observational studies are available that describe gait characteristics in COPD versus non COPD older adults (De & Bhuniya 2015) and systematic reviews have substantiated increased gait variability to be a falls risk in the COPD population (Gillain et al. 2018; Marques et al. 2017).

A promising and emergent area of research in the domain of COPD and falls is the challenge to establish a consensus on which spatiotemporal gait measures are most reliable in differentiating between fallers and non-fallers and how these measures should be conducted in a clinical setting.

Increased variability in stance and stride time has been convincingly observed in the COPD population (Lahousse et al. 2015) and is probably a good indicator of increased falls risk when walking (Heraud et al. 2018; Lahousse et al. 2015; Liu et al. 2017). Yet, these findings are still to be verified at the level of systematic analysis and review and no data on minimal clinically important difference is in circulation. Another shortfall in the available research is the fact that most gait analysis is performed at self-selected velocity or at set velocities above and below self-selected pace. This observation method does not match real life situations or even common clinical practice. Consequently, this is the first study designed to measure gait variations at or near maximum exertion in a way that can easily be replicated in a clinic setting.

An imperative clinical question is addressed in this thesis, the question of how gait variance responds to raised exertion levels. This research question is particularly relevant as currently there is a paucity of COPD research giving clear direction on which gait parameters might change at different exertion intensities. Exertional walk tests have long been reported in systematic reviews as safe, used routinely for exertion testing and are useful for staging and prognostication in COPD (Andrianopoulos et al. 2015; Ho & Maa 2016). Despite this, prior to this current piece of research, it has not been established if walking at or near maximum levels of exertion results in altered gait regularity. The benefit of combining the utility of gait assessment technology and exertion monitoring is that it may provide guidance on early detection of falls risk, give direction on safer exercise testing and therapy methods, and deliver deeper insight into which areas of gait and exertion are most closely related.

Definition and magnitude of COPD

Chronic Obstructive Pulmonary Disease (COPD) is a "lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible" (WHO 2015a; World-Health-Organisation 2015). It is a collective term describing chronic inflammation of the central airways and may predominantly involve emphysema and chronic bronchitis disease processes (WHO 2015a; World-Health-Organisation 2015). The lung disease is considered:

- **Preventable**: COPD is believed to be caused by smoking tobacco (estimated cause of 40% to 70% of COPD cases) and exposure to air pollution (WHO 2015a; World-Health-Organisation 2015);
- **Treatable**: Pharmaceutical and non-pharmaceutical management aims are to reduce risk factors, minimise symptoms and infective exacerbations, and prevent secondary complications (Lisy, White & Pearson 2014); or
- **Incurable**: The disease is progressive and a leading cause of death globally (Lozano et al. 2012; Vogelmeier et al. 2017).

Diagnostic criteria COPD

Spirometric measurement of airflow limitation has been used as one of the key diagnostic criteria for COPD (*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 REPORT* ; Halbert et al. 2006; Vollmer et al. 2009). Because severity of airflow limitation has only a weak correlation with disease symptoms and health status (*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 REPORT*)the Global Initiative for COPD uses four key aspects of the disease to assesses the disease impact, these are:

- The presence and severity of the spirometric abnormality
- Current nature and magnitude of the patient’s symptoms
- History of moderate and severe exacerbations and future risk
- Presence of comorbidities

(*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 REPORT*). Spirometric values, taken after an adequate dose of an inhaled bronchodilator, are used to classify the severity of airflow limitation and a post-bronchodilator fixed ratio of Forced Expiratory Volume in 1 second / Forced Vital Capacity (FEV_1/FVC) < 70 is the recognised benchmark to determine airflow obstruction (Mirza et al. 2018), airflow limitation is then categorised into four levels based on FEV_1 impairment (Table 2.1). Restricted airflow and infective exacerbations of COPD are thought to be responsible for the well-noted exercise impairment of the cohort (Vogelmeier et al. 2017).

Table 2.1 Classification of airflow limitation severity in COPD

Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV_1) in patients with $FEV_1/FVC < 0.70$:		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

(Mirza et al. 2018)

Prevalence, morbidity impact, and mortality of COPD

COPD is a prevalent and widespread condition affecting populations worldwide, with an estimated prevalence of 251 million cases of COPD globally in 2016 (Mathers & Loncar 2006). Globally, it is ranked as the fourth leading cause of death (Mirza et al. 2018), and despite possible under-reporting (Halbert et al. 2006), COPD is predicted to become the third largest cause of death by the year 2020 (Vogelmeier et al. 2017). COPD is an important global health problem that is a major cause of morbidity and mortality. Many people suffer directly from the disease, from secondary comorbidities, and have increased risk of early mortality (Mirza et al. 2018).

The morbidity impact of COPD is substantial both nationally and internationally. In Australia, COPD has been identified as the third leading cause of disease burden (Brooke 2013). Internationally, in the year 2015, COPD accounted for 2·6% of global disability-adjusted life years (Soriano et al. 2017). Multimorbidity in COPD is prevalent with most people having at least one other comorbidity and many having multiple (Vanfleteren et al. 2013). COPD has complex interactions with other comorbidities and is likely to contribute to falls (Hanlon et al. 2018). A cross-sectional study in the

UK of community-dwelling adults (COPD n= 8317; no COPD n= 494 323) found multimorbidity (≥ 4 conditions) to be present in 17% of those with COPD versus 4% in those without COPD (Hanlon et al. 2018). Multimorbidity is likely to contribute to disease severity and mortality, and it increases with age (Hanlon et al. 2018).

COPD is a major cause of mortality globally, and deaths from COPD have been increasing over the past 30 years (Yohannes et al. 2016). In Australia, COPD is placed fifth in the leading causes of death (Brooke 2013). Internationally, an estimated 3.2 million deaths were caused by the disease in 2015 (5% of all deaths globally), which is an 11.6% increase from the year 1990 (Soriano et al. 2017). Patients with COPD have high mortality rates and falls in COPD are an established predictor of mortality risk (Yohannes et al. 2016). A one-year mortality rate study of 898 patients with severe COPD who received inpatient care at a rehabilitation hospital, documented over one year, had an all-cause mortality rate of 22% (Yohannes et al. 2016). A regression analysis revealed that having a history of falls in the 6 months preceding and dyspnoea during activities were predictors of morbidity (OR= 3.05; 95%CI: 1.40 to 6.66; P= ≤ .005) and mortality (OR= 1.05; 95%CI: 1.02 to 1.08; P≤ .002) respectively (Yohannes et al. 2016).

Acute Exacerbation Episodes of COPD

An exacerbation of COPD is an acute worsening of respiratory function that requires more therapy (*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 REPORT*). The worsening of respiratory symptoms includes increased dyspnoea, cough, sputum production and sputum purulence (Kim & Aaron 2018). Acute exacerbations of COPD are classified:

- **Mild** – if treated with short-acting bronchodilators only;
- **Moderate** – if treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids; or

- **Severe** – if the patient visits the emergency room or requires hospitalisation because of an exacerbation (Vogelmeier et al. 2017).

Most exacerbations are triggered by viral infections, but exacerbations can also be initiated or worsened by bacterial infection, air pollution, or climate changes (*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 REPORT*). The causes of acute exacerbations of COPD (and estimated prevalence) include: viral infection (30-60%), bacterial infection (30-50%), eosinophilic inflammation (20%), congestive heart failure (6-8%), pneumonia (6-8%), poor medication adherence (5%), and pulmonary embolism (3%) (Kim & Aaron 2018).

Acute exacerbations of COPD are associated with lost work productivity, increased utilisation of healthcare resources, temporary or permanent reductions in lung function and exercise capacity, hospitalisation, and sometimes death (Kim & Aaron 2018). Exacerbations of COPD are associated with increased dyspnoea, reduced muscle strength, balance impairment, and increased risk of falling (Oliveira et al. 2017).

The frequency and severity of respiratory exacerbations are positively correlated with exercise impairment, reduced balance, and lowered stability performance (Alahmari et al. 2014). A prospective study of 73 people with COPD recorded their daily step count over a 12-month period to classify the participants into a frequent exacerbation group (> 2/year) or infrequent (Alahmari et al. 2014). Results demonstrated that mean daily step count fell from a 4154 steps/day baseline to 3673 steps/day during days of exacerbation and that the stepping pace was faster in untreated compared to treated exacerbations (Alahmari et al. 2014). COPD exacerbations are likely to result in physical inactivity, and frequent exacerbations accelerate deconditioning over time (Alahmari et al. 2014). Even mild episodes of acute exacerbation that do not require hospitalisation are associated with reduced activity levels and reduced leg strength (Alahmari et al. 2016). Mean Six-Minute Walking

Distance (6MWD), when measured in 97 episodes of COPD exacerbation, fell significantly from 422 m (when stable) to 373 m (on day 3 post-exacerbation) (Alahmari et al. 2016). In the same study, quadriceps maximum voluntary contraction fell from 32.6 kg to 29.7 kg (Alahmari et al. 2016).

Evidence suggests that balance control is also impaired during episodes of COPD exacerbation. The Berg Balance Scale (BBS), Single Leg Stance (SLS), and Timed Up and Go Test (TUG) were assessed as measures of balance control in 29 people with stable COPD, 17 people with acute exacerbation, and 17 people with matched demographics as a healthy control group (Crisan et al. 2015). The stable COPD and acute exacerbation group were significantly associated with reduced balance control: BBS reduced from 55/56 (control), 53/56 (COPD), and 44/56 (acute exacerbation); TUG increased from 8.6 sec (control), 12.3 sec (COPD), and 15.9 sec (acute exacerbation); SLS reduced from 31.1 sec (control), 17.7 sec (COPD), and 7.2 sec (acute exacerbation) (Crisan et al. 2015). Results from the above studies indicate that people with COPD have reduced exercise capacity, reduced leg strength, and impaired balance particularly during periods of acute exacerbation. It is reasonable to expect that during times of COPD exacerbation the risk of falling is higher.

Falls are an extrapulmonary COPD presentation

Typical pulmonary symptoms of COPD include breathlessness, sputum production and cough (Lisy, White & Pearson 2014). Extrapulmonary effects of COPD influence multiple body systems and have a wide-reaching scope. Extrapulmonary or systemic effects of COPD have been recognised in the COPD literature for over a decade (Agustí et al. 2003). They include exercise limitation, skeletal muscle dysfunction, metabolic dysfunction, and weight loss (Agustí et al. 2003). High accidental falls rates (Roig et al. 2011), poor postural control (Porto et al. 2015) and abnormal gait (Lahousse et al. 2015) are more recent additions to extrapulmonary complications in COPD that have a profound effect on quality of life measures (Arne et al. 2009). The World Health Organisation defines an accidental fall as “an event which results in a person coming to rest inadvertently on the ground or floor or other lower-level" (WHO 2019). The impact of accidental falls in particular, has been demonstrated to be a significant contributing factor to disease burden in COPD (Hakamy et al. 2018).

Exertional walk tests are an important element of COPD assessment and commonly used during pulmonary rehabilitation to ascertain an individual's physical function (Ho & Maa 2016). The Six-Minute Walk Test (6MWT) and Incremental Shuttle Walk Test (ISWT) are the two most commonly used field walking tests and should be used at regular intervals to establish disease severity (Mirza et al. 2018). Clinical walk tests are considered a safe way of evoking exertion, but few studies are available to advise on safe exertional parameters during testing or the impact maximum levels of exertion has on gait variability or stability. As discussed further in this chapter under various sections this area of investigation has clinical significance as it is unknown if there is a threshold point at which increased exertion places people at greater risk of falling.

Falls risk factors in community-dwelling adults

Risk factors for accidental falls in the general population are diverse and can be defined as an "increased susceptibility to falling that may cause physical harm" (Sousa et al. 2017). A systematic literature review on risk factors for falls identified 62 studies describing 50 individual falls risk factors (Sousa et al. 2017). Recognised risk factors for falling in community-dwelling adults cover demographic, environmental, medication, cognitive, physiological, psychological, and socio-economic risks (Table 2.2) (Sousa et al. 2017). Interestingly, COPD is identified as an individual risk factor.

Table 2.2 General Risk Factors for Falls Identified in the Literature

Risk Factors for Falls	
Demographics	**Physiologic**
Age ≥ 65 years*	Change of blood sugar
History of falls*	Vascular disease
Use of assistive device/s	Compromised eyesight
Female *	Comorbidity/Chronic illness*
Environmental	Chronic pain
	Osteoporosis*
Medication	Compromised mobility*
Poly-medication*	Incontinence
Antihypertensive agents	Orthostatic hypotension
Benzodiazepines	COPD*
Cognition	Arthritis
Change in cognitive function	Poor low limb strength
Diminished executive functions	Metabolic syndrome
Psychological	Arterial hypertension
Fear of falling*	Sensorimotor function
Depression	Urinary urgency
Anxiety	Difficulty in gait*
	Compromised balance
	Vitamin D insufficiency
	Obesity
	Dizziness

*Risk factors more common in COPD
Adapted from Sousa et al. (2017)

Gait variability and velocity as fall predictors in community-dwelling adults

Aberrant spatiotemporal stride-to-stride fluctuations have a positive association with increased risk of falling (Hausdorff, Rios & Edelberg 2001) and appear to worsen with age (Callisaya et al. 2010). A systematic review to assess the utility of accelerometric methods to identify older adults at risk of falling yielded ten cross-sectional studies and identified people that are at risk of falling as those who walk slower, walk with shorter steps, have lower step frequency, have worse stride and step regularity in terms of time, position and acceleration profiles (Gillain et al. 2018). A systematic review of the spatiotemporal parameters of gait capable of distinguishing an elderly faller from a non-faller has likewise been conducted (Mortaza, Abu Osman & Mehdikhani 2014). Results from this review identified fallers to have slower walking speed and cadence, longer stride time, and double support duration, shorter stride and step length, wider step width, and more variability in spatiotemporal parameters in gait (Mortaza, Abu Osman & Mehdikhani 2014). Gait speed per 0.1 m/s decrease has an elevated Risk Ratio (RR= 1.07; 95%CI: 1.00 to 1.14) for falling (Verghese et al. 2009).

Falls in COPD

Prevalence of falls in COPD

The COPD population has a much higher falls rate and rate of repeat falls than matched community-dwelling adults (Ambrose, Paul & Hausdorff 2013; Bozek et al. 2019; Hakamy et al. 2018; Oliveira et al. 2015; Sousa et al. 2017). Community-dwelling adults typically have a falls rate of 29 to 33% (Bongue et al. 2011; Tromp et al. 2001), but if grouped by specific disease, classification can increase to 54% (Delbaere et al. 2010). Rates of repeat fallers in community-dwelling adults are estimated at 10 to 20% (Gregg, Pereira & Caspersen 2000). A large United Kingdom primary health database study found those with COPD to be 55% more likely to have a health record of a fall than non-COPD (Hakamy et al. 2018) and to have a larger rate of repeat falls as the falls incidence per 1000 person-years was 44.9 (95%CI: 44.1 to 45.8) in COPD compared to 24.1 (95%CI: 23.8 to 24.5) in non-COPD (Hakamy et al. 2018). Further evidence of this trend can be found in a twelve-month prospective study which found 40% of community-dwelling adults with stable COPD fell and 75% of the COPD fallers had frequent falls (Oliveira et al. 2015). Other studies estimate falls prevalence in community-dwelling adults with COPD to be between 44 and 51% (Beauchamp et al. 2009; Beauchamp et al. 2012; Roig et al. 2011).

Injury and bone fracture from falling in COPD

The rate of severe injuries such as fragility fractures are more prevalent in COPD than community-dwelling adults (Huang et al. 2016; Jorgensen et al. 2014; Yamauchi et al. 2016) and is a substantial contributor to disease burden. Fractures of the hip are the most common fracture site leading to admission to hospital in COPD, and the high rate of hip fracture in COPD is important as it has a stronger association with mortality than other fracture types (Yamauchi et al. 2016). Jorgensen et al. (2014) give an incidence rate ratio for hip fracture and proximal humeral fracture in COPD of 1.43 (95%CI: 1.39 to 1.46) and 1.24 (95%CI: 1.19 to 1.29) respectively. Huang et al. (2016) give a covariate-adjusted hip fracture hazard ratio of 1.57 ($P= \leq .001$). A large retrospective study of patients admitted with a primary diagnosis of hip fracture over a 10-year period (2004 to 2013) found hip fracture cases per 100,000 increased from 312 to 427 (115 cases) in those with COPD, and from 284 to 314 (30 cases) in those without COPD (de Miguel-Diez et al. 2016). Hip fracture is more prevalent in those with COPD than those without and accounted for 6.9% of those admitted with hip fracture (de Miguel-Diez et al. 2016).

A high rate of bone fracture from accidental falls in COPD may be due to a high co-presentation of osteoporosis (Corsonello et al. 2011; Lu et al. 2017). A 2002 review gave the prevalence of osteopenia in COPD to be 35 to 72% and osteoporosis at 36 to 60% (Biskobing 2002). A more recent systematic review in 2009 gave the prevalence of osteoporosis and osteopenia to be 9–69% and 27–67% respectively in COPD (Graat-Verboom, Wouters, Smeenk, et al. 2009). The fracture rate of COPD people who fall is 36.3% compared to 7.3% in age- and gender-matched healthy adults (Gazzotti et al. 2019). Authors of the study attribute the high rate of fracture to the high prevalence of osteoporosis in the COPD group, as they found 29.7% of those with COPD to have a co-presentation with osteoporosis, compared to only 18.3% in the control group ($p= .007$) (Gazzotti et al. 2019).

The high prevalence of osteoporosis in COPD is associated with the prescribed dose of steroid used to manage the condition and the duration of exposure to the drug (Lu et al. 2017). The use of oral corticosteroids with a large cumulative defined daily dose has a hazard ratio for developing osteoporosis of 1.85 (95%CI: 1.52 to 2.26) (Lu et al. 2017). Lu et al. (2017) reports an incidence of osteoporosis in people with COPD as 1,343 per 100,000 person-years but this rate varies between studies. The dose and duration of steroid medication exposure may explain the discrepancy in the reported incidence of osteoporosis and osteopenia in COPD and why the amount of volumetric bone mineral density loss increases as the disease progresses. Jaramillo et al. (2015) found 58% of people with COPD to have low bone mineral density versus 84% in those with very severe COPD. It is likely that as the disease progresses, the exposure and dose of inhaled corticosteroids increases, while at the same time weight-bearing activity decreases. To compound this effect, deconditioning processes may increase the risk of falling.

COPD specific risk factors for falling

Demographic risk factors for falls in COPD

The COPD demographic is an older-adult population, and disease severity typically worsens with age due to the cumulative effect of repeated exposure to air contaminants (Mercado, Ito & Barnes 2015). According to a large cross-sectional study (> 200,000 households over eight countries), the mean age of people with COPD is 63.3 years, 55.8% of whom were male and 44.2% female (Rennard et al. 2002). A more recent study (surveying > 100,000 households across twelve countries) showed that females are now more likely to have COPD than males (52% vs 48% respectively) and that the age of onset is dependent on geographic location (Landis et al. 2014). The combined summary of these papers is that average COPD age is decreasing and the proportion of females with COPD is increasing. Both these factors are important, as both older age and female sex are risk factors for falling (Sousa et al. 2017).

Medication risk factors for falls COPD

Polypharmacy has been established as an independent falls risk factor (Sousa et al. 2017). Prescription of multiple medications is associated with multimorbidity, is more common in older adults, and can be listed as appropriate or inappropriate polypharmacy (Masnoon et al. 2017). There is no accepted definition of polypharmacy, but a systematic review of polypharmacy definitions indicates the consensus number of prescribed medications is more than or equal to five medications (Masnoon et al. 2017). A prospective study of falls in people with COPD identified those that take multiple medications to have an incidence rate ratio of 1.15 (95%CI: 1.00 to 1.34) falls per person-years (Oliveira et al. 2015). This finding is supported by a matched cohort study of a United Kingdom primary care database in which COPD was reported to have higher rates of multimorbidity (17% compared to 4% in non-COPD) and higher levels of polypharmacy (52% with COPD compared to 18% in non-COPD) (Hanlon et al. 2018). Interestingly, a large study investigating determinants to poor adherence to pharmacological treatment discovered that 59.5% (n= 13381) of the COPD participants were taking ≥ 5 medications, and polypharmacy was positively associated with poor adherence to prescribed medication regimens in the persons ≥ 65 years old (OR= 1.34; 95%CI: 1.13 to 1.59) (Vetrano et al. 2017).

The type of medications people take, and the interactions between medications also influence the risk of falling (Ambrose, Paul & Hausdorff 2013). A literature review of risk factors for falling in older adults identified psychotropic medications, diabetes medications (for increased risk of traumatic fracture), nonsteroidal anti-inflammatory drugs, cardiovascular medications, antiepileptics and medications for depression as factors that increase likelihood of accidental falls (Ambrose, Paul & Hausdorff 2013). A more recent literature review on medications associated with risk of falling found the following classes of prescription medications to be associated with falls in the general older population: sedatives, hypnotics and antidepressants, including tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors (Park et al. 2015). Both reviews above site mood-altering medication for the treatment of depression as a medication class associated with falls. This finding is important in the COPD population as depression prevalence in COPD can be as high as 80% (Pollok, van Agteren & Carson-Chahhoud 2018) and more than one third can experience depression and anxiety (Panagioti et al. 2014).

There is a lack of studies designed specifically to investigate the role of polypharmacy or the use of specific types of medications in relation to increasing the risk of falling in COPD, however high rates of polypharmacy is identified in the COPD cohort (Hanlon et al. 2018). A cross-sectional survey study collected baseline assessment data from 502,640 community-dwelling participants aged 37 to 73 to evaluate the pattern and extent of multimorbidity and polypharmacy in COPD group (Hanlon et al. 2018). This study found participants with COPD (n= 8317) were significantly more likely than those without (n= 494,323) to be prescribed ≥ 3 medications contributing to a greater risk of reporting adverse drug reactions including falls (OR 2.27; 95%CI: 2.13 to 2.42) (Hanlon et al. 2018). In the same study, authors state that those with COPD were more likely to take multiple medications and have adverse drug reactions than any other chronic condition category.

Medications required for effective management of COPD appear to contribute toward, but not be solely responsible for, all skeletal problems in COPD. Sex, older age, and use of a high oral corticosteroids dose increased the risk of osteoporosis with a hazard ratio of 1.85 (95%CI: 1.52 to 2.26) (Lu et al. 2017). Fragility fractures from low bone mass is common in COPD, but medication use is not the only risk factor associated is osteoporosis in this cohort (Misof et al. 2016). Risk factors other than medications include systemic inflammation, tobacco smoking, and vitamin D deficiency (Misof et al. 2016). Despite the existence of multiple risk factors, glucocorticoids and other corticosteroids are common frontline medications for both maintenance and management of exacerbations, and they appear to be a strong contributor to bone changes in COPD (Misof et al. 2016).

Physiological risk factors for falls in COPD

Physiological risk factors for falling validated in non-respiratory conditions such as lower limb weakness and reduced postural control (Roig et al. 2009) are also prevalent in the COPD population. Multiple body systems required for safe and stable locomotion are impaired in COPD. Factors listed to be associated with impaired postural control and falls in COPD include muscle weakness, physical inactivity, older age, need for supplemental oxygen, and limited mobility (Porto et al. 2015). Severity of oxygen dependency (Roig et al. 2011), dyspnoea and impaired balance (Beauchamp et al. 2009; Ozalevli et al. 2011), activity avoidance and deconditioning (Hellstrom et al. 2009), as well as gait impairment (De & Bhuniya 2015) are all associated with falling in COPD. Fallers with COPD have impaired gait rhythm which is an impairment that is positively correlated with severity of airflow limitation and high frequency of infective exacerbations (Lahousse et al. 2015). Gait impairment has emerged as a reliable predictor of falls in COPD (Zago et al. 2018). Each of the above physical risk factors for falls is explored in more depth in the following sections.

Morbidity and disease burden associated with falls

Many chronic diseases are independently associated with a high incidence of accidental falls and the presence of multiple chronic diseases is considered a falls risk factor (Paliwal, Slattum & Ratliff 2017). A cross-sectional survey study found chronic disease to be an important predictor of falling and ranked COPD second among common chronic diseases associated with falling (Lawlor, Patel & Ebrahim 2003b). Accidental falls contribute significantly to disease burden in COPD.

Multimorbidity as a risk factor for falling in COPD

Multimorbidity is defined as “the co-occurrence of two or more chronic medical conditions in one person” (WHO 2015b) and is a recognised risk factor for injurious falls in older adults (Tchalla et al. 2014). COPD is often accompanied by other chronic diseases and perhaps co-present because of common risk factors such as tobacco smoking, inactivity and aging, all of which can lead to significant morbidity, mortality and economic burden (Lisspers et al. 2018). Interactions between multimorbidity clusters (common morbidity group configurations) have been shown to extend the impact of each individual disease process (Tchalla et al. 2014). Multimorbidity is prevalent in COPD (Anecchino et al. 2007; Hanlon et al. 2018) and has been recognised as a risk factor for falls, increasing falls, and has been associated with chronic recurring falls (Tchalla et al. 2014).

Historically, the impact of COPD has been measured by the number of visits to a physician, emergency department presentations or hospitalisations (Mirza et al. 2018). These measures are inadequate in capturing the effect of multimorbidity clusters such as cardiovascular disease, musculoskeletal impairment and diabetes mellitus (Vanfleteren et al. 2013). A systematic review of the prevalence of osteoporosis and osteopenia in COPD found 35% of people with COPD are likely to have osteoporosis (Graat-Verboom, Wouters, Smeen, et al. 2009). Osteoporosis and sarcopenia are important and common comorbidities in COPD (Vespasiani-Gentilucci et al. 2018), and the impact of osteoporosis in COPD is reflected in the increased incidence of fractures (Romme et al. 2015). People with COPD have higher rates of mortality from hip fracture than other types of bone fracture (Yamauchi et al. 2016).

COPD is commonly co-present with osteoarthritis, osteoporosis, or type two diabetes myelitis, and produces a disease relationship that is likely to compound falls risk factors, increase the potential for accidental falls, and result in injury (Holland, Harrison & Brooks 2016). COPD and hypertension also form a multimorbidity cluster group found to have high falls rates, but further investigation is required to study the complex interactions between other chronic health conditions (Paliwal, Slattum & Ratliff 2017). It is likely that impaired postural control and cerebral hypoxemia are factors which lead to increased prevalence of falls in people with the co-occurrence of COPD and hypertension (Paliwal, Slattum & Ratliff 2017). As COPD has a high prevalence of multimorbidity, it is associated with increased polypharmacy, leading to an increased potential for adverse drug reactions (Hanlon et al. 2018). Polypharmacy alone increases the risk of accidental falls (Sousa et al. 2017), but combined with co-occurrence of chronic disease may further compound falls risk.

Gait impairment and falls risk in COPD

Abnormal gait speed in COPD

Gait speed and variability is a falls predictor that is prevalent in COPD

Increased gait variability (Marques et al. 2017) and reduced self-selected walking velocity (Abu Samah et al. 2016) are fall predictors identified in older adults and exist more extensively in the COPD population than in healthy adults (Lahousse et al. 2015). Cross-sectional prospective studies have described COPD fallers as people who walk slower, more frequently use an assistive device to ambulate, and typically fall while walking outdoors (Roig et al. 2011). These findings are important as reduced gait speed (below 0.6–1.0 m/s) is a standalone gauge for identifying the increased probability of falling in older adults (Abu Samah et al. 2016) and associated with survival (Studenski et al. 2011). A large pooled analysis of nine cohort studies using data from community-dwelling adults over 65 years old show survival increases with gait speed (Studenski et al. 2011). In the context of this finding it is important to note that walking velocity impairment becomes more pronounced as COPD severity progresses (Bousquet et al. 2016; Karpman & Benzo 2014), it is therefore reasonable to infer that as COPD severity progresses, gait quality deteriorates and risk of falling increases.

Gait speed reduces with COPD severity, indicating a progressive falls risk

Studies of gait speed in COPD participants indicate that the velocity of walking reduces as COPD severity increases (Ilgin et al. 2011; Iwakura et al. 2019; Karpman & Benzo 2014) and that frequency of frailty increases (Mittal et al. 2016). In a large observational study, gait speed using the 6MWT was measured and compared with lung function assessment (Ilgin et al. 2011). Mean gait speed of controls and those with mild COPD were significantly slower than in participants in the moderate (75.7 m/min), severe (64.3 m/min), and very severe (60.2 m/min) COPD groups (Ilgin et al. 2011). Slower gait speed was also significantly correlated with increasing dyspnoea, and poorer scores on a questionnaire-based health survey (Ilgin et al. 2011). The consequence of decreasing gait speed with disease progression is increased risk of falling at a stage of the disease where frailty is increasing, which further increases the potential for injury, such as a bone fracture. A study of the correlation between gait speed and the presence of frailty in those with COPD revealed that mean gait speed was 0.95 m/s in robust participants and 0.68 m/s in frail participants, and that gait speeds slower than 1 m/s had a 95% sensitivity to predict frailty (Mittal et al. 2016).

Self-selected walking speed in COPD appears to be limited more by a sensation of dyspnoea and leg fatigue than an increase in walking oxygen consumption (Sanseverino et al. 2018). A study aimed at comparing the economy of walking and gait variability as a function of speed in COPD relative to healthy subjects used six treadmill walking speeds and measures of oxygen consumption normalised by mass and distance (Sanseverino et al. 2018). The walking speeds selected were self-selected, two speeds above, two below, and a fixed speed of 0.89 m/s. Walking economy in the control group was at its maximum at the self-selected speed, and economy of walking (oxygen consumption over speed) worsened at speeds above this speed (Sanseverino et al. 2018). Conversely, the COPD group had increased gait variability and worse economy of walking at slow walking compared to faster walking (Sanseverino et al. 2018). Dyspnoea and leg fatigue in the COPD group increased above the self-selected walking speed (Sanseverino et al. 2018). Supporting these results, a comparison study between healthy and COPD participants walking at their preferred speed and ± 20% preferred speed demonstrated those with airflow obstruction had reduced energy efficiency with a greater frequency ratio of strides to breaths (Yentes et al. 2019).

Spatiotemporal measures of gait are impaired in COPD

A systematic literature review to evaluate the current understanding of spatiotemporal, kinematic and kinetic gait features in patients with COPD identified the predominant gait abnormalities to be reduced step length and cadence, increased variability of spatiotemporal parameters, and to a smaller degree subtle biomechanical changes at the ankle level leading to reduced foot stability after the foot first lands (Zago et al. 2018). Despite these gait features being identified in COPD, authors of the review identified a lack of research describing a persuasive mechanistic link between the listed gait impairments and a high incidence of falls in COPD (Zago et al. 2018). Since 2009, it has been identified that further research is required to identify mechanistic links between gait disturbance, balance impairment, and falls in COPD (Roig et al. 2009). However, since this early research occurred only a limited number of studies have been conducted in this area and further research is required to substantiate and describe gait impairment in COPD as it relates to falls (Zago et al. 2018). A systematic review aimed at understanding the spatiotemporal characteristics of gait in COPD found a scarcity of studies, small sample sizes, and pooling of gender and disease status as the main limitations to identifying a causal link between gait impairment and falls in COPD (Zago et al. 2018). Despite these limitations, the evidence available indicates that people with COPD have impairment in most spatiotemporal measures of gait (Liu et al. 2017), and that the level of gait impairment increases with disease severity (Lahousse et al. 2015).

Step time, step width, and step length variability are impaired in COPD

The increased variability or reduced regularity of step time, width and length may indicate an increased risk of falling in COPD (Morlino et al. 2017; Rutkowski et al. 2014; Yentes et al. 2017; Yentes et al. 2015). Step time is measured as the duration that passes while one extremity is on the supporting surface in a gait cycle; step width is measured as the distance between two supporting steps; and step length is the distance from the point of contact of the heel print of one foot to the point of contact of the heel print of the opposite foot (Yentes et al. 2015). Gait evaluation during a 6MWT in those with COPD and matched healthy controls identified those with COPD to have impaired stance time (left MD= 0.58%, p= .002; right MD= 0.57%, p= .003) and step length (left MD= 1.77%, p= ≤.001; right MD= 1.74%, p= ≤.001) independent of self-selected walking speed (Liu et al. 2017). A similar study corroborating this result found COPD participants over a 6MWT had shorter step length and longer step time than controls (Rutkowski et al. 2014). Both studies had a small participant number and did not stratify by disease severity. An observational study identified increased step length variability during a 6MWT to be associated with impaired balance but not FEV_1 or hypoxemia (Morlino et al. 2017). This result may indicate that increased gait variability may result from more chronic changes than transient respiratory changes resulting from walking with exertion.

Stride time and length variability is impaired in COPD

Stride time and stride length variability may be increased in COPD and be an indicator of increased fall risk when walking (Heraud et al. 2018; Lahousse et al. 2015; Liu et al. 2017). Stride time measures the duration between the first foot contact with the ground in two consecutive footsteps of the same foot whereas stride length is the distance between successive ground contacts of the same foot. A small comparison study found stride time variability to be more irregular in COPD group than in control group, and a gait distinction that remained after participation in pulmonary rehabilitation (Heraud et al. 2018). Another small comparison study found those with COPD to have more stride length variability than controls, irrespective of self-selected walking velocity or quadriceps strength (Liu et al. 2017). Both step time (Lahousse et al. 2015) and step length (Liu et al. 2017) variability appear to increase in a corresponding pattern with disease severity.

Gait rhythm (stride time variation) in COPD is impaired compared to healthy populations (Annegarn et al. 2012; Lahousse et al. 2015); it is also a predictor of falls and positively correlated with airflow limitation (Annegarn et al. 2012; Lahousse et al. 2015). In a 6MWT gait analysis, those with COPD have reduced walking-intensity, slower cadence and greater gait variability than healthy participants (Annegarn et al. 2012). This finding is supported by a large cohort study (the Rotterdam study) in which gait rhythm variability, phases, pace, tandem, turning and base of support were measured on an electronic walkway (Lahousse et al. 2015). Presence of COPD was found to be associated with lower rhythm (independent of age, sex and height), and lower FEV_1 was significantly associated with variable rhythm, cadence and gait velocity (association remained after adjustment for cognitive impairment) (Lahousse et al. 2015). Another important finding of the Rotterdam study is that people with COPD and a history of falling had significantly worse rhythm than non-fallers with COPD (Lahousse et al. 2015).

Double support time is impaired in COPD

It is likely that people with COPD have increased time spent in double support phase of their gait (Nantsupawat et al. 2015) and have increased spatiotemporal variability in their overground gait patterns than matched healthy adults (Liu et al. 2017). Double support time is the duration spent with both feet contacting the ground during one gait cycle, and the percentage of time spent in double support time reduces as gait velocity increases. A Gait Real-time Analysis Interactive Lab based 6MWT was conducted on 80 COPD participants and 38 healthy controls to compare differences in gait patterns between the groups (Liu et al. 2017). COPD participants had significantly increased variability in double support time (MD= 1.18%, $p = .001$) (Liu et al. 2017).

Mechanisms of gait impairment in COPD

Some of the suggested mechanisms for gait impairment found in recent studies include fatigue from deconditioning, changes in the central processing of balance and coordination (Morlino et al. 2017), and reduced ability to deliver oxygen to peripheral muscle tissue (Medeiros et al. 2014). There is no conclusive evidence giving the exact mechanism which leads to gait impairment in COPD, and there is only a small number of studies available that investigate the mechanisms of gait impairment.

Fatigue and gait in COPD as a mechanism for gait impairment

There is some evidence that fatigue in people with COPD may produce increased gait variability (Yentes et al. 2015). A small study aimed at determining the presence of biomechanical gait abnormalities in COPD patients (compared to healthy controls) in the condition of rested versus fatigued found that the COPD group increased their gait speed and stride length when transitioning from rest conditions to fatigue conditions (Yentes et al. 2015). Also, the control group had an associated peak ankle dorsiflexion moment in the transition, whereas the COPD group remained constant ($p = \leq 0.01$) (Yentes et al. 2015). This finding is important, as step width variation is associated with increased risk of falling (Brach et al. 2005). Those with COPD compared to matched controls have lower leg muscle mass (mean= 8.0 vs. 8.9 kg, respectively) and produced relatively lower absolute and leg muscle mass normalised torque ($p = \leq .05$) (Medeiros et al. 2014). Consequently, COPD participants needed greater fractional O_2 extraction to produce torque compared to controls, indicating that O_2 delivery to peripheral skeletal muscle is impaired in COPD (Medeiros et al. 2014) and is a possible mechanism of reduced muscle performance.

Cognitive impairment in COPD as a mechanism for gait impairment

Cognitive impairment and executive function loss are independently associated with increased falls risk, fall-related injuries, and decreased physical function in community-dwelling older adults (Muir et al. 2013). To establish the epidemiological link between cognitive impairment and fall risk, a systematic review and meta-analysis of twenty-seven studies identified impairment of global measures of cognition to increase risk of fall and injury with an OR= 2.13 (95%CI: 1.56 to 2.90) (Muir, Gopaul & Montero Odasso 2012). Community-dwelling older adults with even subtle executive function impairment have an increased risk of fall (OR= 1.44; 95%CI: 1.20 to 1.73). There is ongoing investigation into which cognitive functions have the most significant impact on the risk of accidental fall (Muir, Gopaul & Montero Odasso 2012).

There is a sparsity of studies that directly correlate measures of cognition with falls incidence in the COPD population, however cognitive impairment and degradation of executive function have been demonstrated to be prevalent in the COPD cohort (Charbek et al. 2019). A cross-sectional study of people with COPD attending a pulmonary ambulatory clinic (n= 106) underwent cognitive assessment and cognitive classification (Charbek et al. 2019). Results showed that 36 (33.9%) participants were classified with dementia, 33 (31.1%) had mild cognitive impairment, and 37 (34.9%) had normal age-appropriate scores. A reasonable inference is that cognitive impairment (an established risk factor for falls) is a contributing factor to the high prevalence in falls because of its pervasiveness in this population, yet further investigation is required to establish and clarify this link.

The occurrence of cognitive impairment in COPD is more prevalent than in age-matched healthy adults (Lawi et al. 2018) and is one possible mechanism for reduced exercise capacity and increased gait variability (Morlino et al. 2017; van Beers et al. 2018). Hypoxemia, chronic inflammation, dietary insufficiencies, reduced physical activity, comorbidity, obstructive sleep apnoea and depression are risk factors for cognitive impairment that are often present in COPD (van Beers et al. 2018). Cognitive impairment, and in particular executive functioning, is positively associated with reduced exercise capacity and COPD disease severity (Randeep et al. 2019). A small study of 40 COPD participants and 28 control participants correlated measures of lung function, Mini-Mental State Examination (MMSE) and dynamic balance to assess the influence of respiratory versus cognitive processes on dynamic balance performance (Morlino et al. 2017). Although proximal muscle strength was reduced in COPD, there was no significant correlation with lung function, mental state, or balance (Morlino et al. 2017). Gait speed in the 6MWT was significantly correlated with poor balance and poor lung function; the COPD group also had significantly lower MMSE scores than controls ($p= \leq .025$) (Morlino et al. 2017). Authors of this study suggested that balance impairment is more directly related to central mechanisms such as central nervous lesions.

Balance control impairment and falls risk in COPD

Many common measures of balance are impaired in COPD (Beauchamp et al. 2012; De Castro et al. 2016; Jácome et al. 2016). The impairment appears to worsen at times of acute infective exacerbation (Crisan et al. 2015; Oliveira et al. 2017) and may be related to increased frequency of accidental falls (Oliveira et al. 2017; Ozalevli et al. 2011). Both static and dynamic balance are impaired in COPD cohorts across the spectrum of disease severity (De Castro et al. 2016). People with COPD have worse BBS scores, reduced SLS time, and slower TUG tests than healthy adults (Crisan et al. 2015). The severity of balance impairment positively correlates with increased risk of falling and is useful as a predictor of falls (Beauchamp et al. 2009). Balance impairment appears to be moderated by participation in pulmonary rehabilitation (Beauchamp et al. 2010; Mkacher et al. 2015), but it is unproven if increased levels of exertion increase balance impairment, making those with COPD more at risk during exercise testing.

Balance impairment is common in COPD

Balance impairment is common in COPD (Porto et al. 2015); it increases with COPD severity (Crisan et al. 2015) and may be more pronounced in the bronchitic dominant phenotype (Voica et al. 2016) but there is no consensus agreement on the exact mechanism leading to balance impairment.

Mechanisms leading to balance impairment are under researched and are probably multifactorial. A systematic review of studies evaluating postural control as a primary outcome in COPD identified significant postural control impairment compared to age-matched healthy controls (Porto et al. 2015). There is some evidence to suggest that the COPD phenotype may also impact on balance performance, because the different phenotypes characteristically have different body composition and muscle mass (Voica et al. 2016). A small-sized study showed people with the bronchitic type COPD to have worse scores in Activities-specific Balance Confidence Scale (ABC), BBS, TUG test, SLS time, and 6MWT distance compared to people with emphysematous type COPD (Voica et al. 2016).

The exact pathophysiology of the balance impairment in the bronchitic subgroup is unknown, it is postulated that body weight distribution, poor exercise capacity, hypoxemia, skeletal muscle atrophy and high BMI are contributing factors to worse balance performance (Voica et al. 2016). An alternative mechanism thought to contribute to impaired balance control is the effect chronic cough has on pelvic floor muscles, core stability and the ability to regulate intrathoracic and intra-abdominal pressures (Massery 2009). Unfortunately, there are few studies available to establish this as a contributing factor in reduced balance performance. A search of the Scopus database using the key words ‘chronic cough’, ‘postural control’, ‘falls’, ‘balance’, ‘pelvic floor’ yielded no randomised control trials relevant to this area. One exception is a small study that identified Otago exercise program intervention combined with pelvic floor muscle training was more effective than pelvic floor muscle training delivered as a control (Yuvarani et al. 2019). Limitations of this study include small size and the use of falls predictive measures rather than fall risk ratio data.

Balance assessment is a predictor of falls in COPD

Body balance control requires the ability to maintain the bodies centre of mass within perimeter of support (Shumway-Cook & Woollacott 2007), it can be measured using various clinical tools and can be used to discriminate between COPD fallers and non-fallers (Beauchamp et al. 2009; Ozalevli et al. 2011). A cross-sectional study of adults over 60 years old with COPD used baseline measurements of balance and a one year falls diary to conclude that standard clinical measures of balance could discriminate between fallers and non-fallers in COPD (Beauchamp et al. 2009). In this study, 46% of the COPD participants sustained a fall; fallers had worse mean BBS than non-fallers of 45.2 (out of 56) versus 48.8 ($p = .042$), and poorer TUG mean time of 17 sec versus 14 sec ($p = .024$) (Beauchamp et al. 2009). In a similar study, Jácome et al. (2016) used the BBS, Balance Evaluation Systems Test (BESTest), Mini-BESTest, and Brief-BESTest assessments to discriminate between COPD fallers and non-fallers. Interestingly, each of the balance tests statistically correlated with each other (Spearman's rank correlation coefficient: 0.73 to 0.90) but the BBS and the Brief-BESTest had the strongest sensitivity and specificity (sensitivity= 73% and 81% and specificity= 77% and 73%, respectively) (Jácome et al. 2016).

Relationship between hypoxemia, hypercapnia, and impaired balance control in COPD

One possible mechanism of loss of stability in the COPD population may be related to central hypoxemia and hypercapnia. COPD falls are more likely to occur in people that are oxygen-dependent (Roig et al. 2011), and balance impairment is more significant during times of infective exacerbation (Crisan et al. 2015; Oliveira et al. 2017). During periods of infective exacerbation, hypoxemia and hypercapnia are more pronounced (Oliveira et al. 2017), and there is a clear positive correlation between dyspnoea, arterial oxygen saturation values, and poor BBS scores along with increased falls frequency ($p \leq .05$) (Ozalevli et al. 2011). A higher falls incidence and larger balance impairment are present in hospitalised patients with an acute infective exacerbation of COPD compared to people with stable COPD (1.76 falls/person/year versus 0.53 falls/person/year, respectively) (Oliveira et al. 2017). The study supports the idea that increased dyspnoea and hypoxemia results in reduced physical activity, strength, stability, and increases the risk of falling (Oliveira et al. 2017).

Despite chronic hypoxemia being associated with reduced balance control and falls, short bouts of exercise-induced hypoxia do not appear to result in accidental fall events during exercise testing.

The 6MWT has been used as the mainstay in function assessment in COPD for decades (Guyatt et al. 1985) and has been proven to be a safe test to administer. Adverse events occur in 6 to 11% of participants, and oxygen desaturation during exercise testing is documented as the most common adverse event in the 6MWT (for people with chronic lung disease), however accidental falls are not reported amongst adverse events (Afzal et al. 2018; Jenkins & Čečins 2011). Jenkins and Čečins (2011) found that 47% of patients with chronic lung disease had a desaturation of more than 4% in SpO_2 to lower than 90% during the 6MWT.

Pulmonary rehabilitation for COPD

Pulmonary rehabilitation is the non-pharmaceutical treatment of choice for COPD (Mirza et al. 2018). A Cochrane review of 65 randomised control trials found participation in pulmonary rehabilitation to be effective in reducing dyspnoea and fatigue (McCarthy et al. 2015) and that pulmonary rehabilitation with a balance component may be effective in mitigation of falls risk factors, as it has a demonstrated ability to reduce incidence and frequency of falls (Cruz et al. 2015; Hakamy et al. 2018; Hill 2014; Mkacher et al. 2015). Pulmonary rehabilitation is known as a safe and effective treatment modality (McCarthy et al. 2015; Puhan et al. 2016) and can be administered even at times of acute exacerbation (McCarthy et al. 2015; Puhan et al. 2016).

Future studies are required to determine which components of pulmonary rehabilitation are indispensable, how much oversight participants should have, and the intensity at which participants should participate (McCarthy et al. 2015). Despite the increasing prevalence of pulmonary rehabilitation treatment, there are few studies designed to directly examine the direct result of raised levels of physical exertion (experienced during pulmonary rehabilitation) on balance control or gait regularity. It is unknown if gait variability or balance control deteriorates at times of increased exertion such as during baseline fitness testing or while participating in pulmonary rehabilitation. If pulmonary rehabilitation programs are to become more selective in screening for physical impairment and tailored to individual needs, there is a lack of existing evidence to guide clinicians on safe and acceptable levels of exertion for participants.

Definition and function of pulmonary rehabilitation for COPD

Pulmonary rehabilitation (otherwise known as respiratory rehabilitation) is typically a six to eight-week program delivered by a range of health professionals and involves comprehensive patient-tailored therapies (Mirza et al. 2018; Puhan et al. 2016). Pulmonary rehabilitation is defined as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours." (Spruit et al. 2013). Components of pulmonary rehabilitation include exercise, education, self-management behaviour change, and adherence to health-enhancing behaviours (Mirza et al. 2018).

Pulmonary rehabilitation is considered gold standard care in COPD treatment and is validated by systematic reviews as the most effective non-pharmaceutical treatment to improve dyspnoea, fatigue, health status, and exercise tolerance (McCarthy et al. 2015). Therapeutic benefits of pulmonary rehabilitation intervention are moderately large, clinically significant (McCarthy et al. 2015; Puhan et al. 2016) and can last up to 12 months post-intervention (Ryrso et al. 2018). The current best care model for COPD is shifting away from a disease-centric approach and is moving towards a patient-centred care paradigm in which interventions such as pulmonary rehabilitation provide treatment for complex presentations with multimorbidity (Holland, Harrison & Brooks 2016). Aims of pulmonary rehabilitation are to optimise function, augment integration across care settings, value-add from multidisciplinary team input, and monitor patient-important outcomes (Holland, Harrison & Brooks 2016). Measures of disease impact in COPD, such as mobility, strength, balance, cognition, nutrition, endurance and physical activity also appear to be improved by participation in pulmonary rehabilitation (Holland, Harrison & Brooks 2016).

Effect of pulmonary rehabilitation on respiratory symptoms in COPD

People with COPD have increased dyspnoea (Ramon et al. 2018), reduced activity levels compared to healthy adults (Albergoni et al. 2019; Saunders et al. 2016), and lower exercise capacity (Blondeel et al. 2018). To investigate the link between dyspnoea and physical inactivity results from a literature search were taken to construct and validate the statistical model. The model commenced with airflow limitation, which lead to hyperinflation and dyspnoea, punctuated by COPD exacerbations, which leads to physical inactivity, and reduced exercise capacity (Ramon et al. 2018). Pulmonary rehabilitation interventions have a treatment effect on reversing reduced exercise capacity and can be implemented close to exacerbations (Puhan et al. 2016; Ryrso et al. 2018). High-quality evidence from a Cochrane review found 6MWT distances to have an average increase of 62 meters (95%CI: 38 to 86) (Puhan et al. 2016). Outcomes from a more recent review and meta-analysis also demonstrated significant improvement in 6MWT and ISWT distances between early pulmonary rehabilitation participation versus usual care ($p= \leq .001$ and $p= \leq .002$, respectively), indicating that early commencement of pulmonary rehabilitation was able to improve exercise tolerance (Ryrso et al. 2018).

Participation in exercise therapy for eight to twelve-weeks (at an unspecified intensity) has been demonstrated to be effective in modifying levels of dyspnoea, reducing fatigue, and improving functional exercise capacity (McCarthy et al. 2015). A 2015 systematic review of randomised control trials (RCTs) on pulmonary rehabilitation and measures of physical functional identified 65 RCTs containing 3822 participants (McCarthy et al. 2015). A meta-analysis of the studies revealed moderate-quality evidence that participation in pulmonary rehabilitation relieves dyspnoea scores by a mean difference of 0.79 units (95%CI: 0.56 to 1.03) and 0.5 units is the recognised minimum clinically important difference (McCarthy et al. 2015). Mean difference in fatigue and maximal exercise capacity were also positively affected by participation in pulmonary rehabilitation – 0.68 units (95%CI: 0.45 to 0.92) and 6.77 units (95%CI: 1.89 to 11.65) respectively (McCarthy et al. 2015).

Exercise components include endurance and strength training of varying intensities and durations, making it unclear which components of pulmonary rehabilitation have the greatest effect in improving shortness of breath, reducing fatigue, and improving exercise capacity (Puhan et al. 2016).

Balance impairment in COPD is mediated by pulmonary rehabilitation

Pulmonary rehabilitation has been demonstrated to be an effective therapeutic intervention to improve strength, exercise tolerance and balance control (McCarthy et al. 2015; Mkacher et al. 2015) and is the intervention of choice to reduce falls risk. Pulmonary rehabilitation with a balance training component is more effective at improving balance control and muscle strength than pulmonary rehabilitation alone (Beauchamp et al. 2013). After just six weeks of combined balance exercises and standard pulmonary rehabilitation, participants receiving combined intervention achieved significantly better results in the BBS ($p = \leq .01$) and BESTest ($p = \leq .01$) than the control group receiving only standard pulmonary rehabilitation (Beauchamp et al. 2013). This study indicates that balance and muscle strength training in COPD can improve balance measures and subsequently reduce falls risk. A limitation of the study is the concept that a statistically significant difference in balance measures does not necessarily equate to a clinically meaningful change in balance.

There is a lack of studies that directly evaluate the effect of pulmonary rehabilitation participation on balance control, but the evidence available is favourable toward positive benefits of pulmonary rehabilitation (Hakamy, Bolton & McKeever 2017). A 2017 systematic review of studies evaluating the impact of pulmonary rehabilitation on balance and falls only identified two cohort studies on balance and no studies that focused solely on falls as an outcome (Hakamy, Bolton & McKeever 2017). The studies identified in the review gave some positive benefits of pulmonary rehabilitation on balance but found the area to be under-investigated (Hakamy, Bolton & McKeever 2017). Balance improvements gained in pulmonary rehabilitation appear to be maintained at least over a twelve-month period unless an acute infective exacerbation of COPD occurs (Harrison et al. 2019).

Effect of specific balance training versus generalised pulmonary rehabilitation on balance in COPD

Balance impairment is prevalent in the COPD population and is an important risk factor for accidental falls (Neumannová et al. 2017), and may have been omitted in traditional pulmonary rehabilitation despite it potentially being a modifiable impairment (Beauchamp et al. 2010; Mkacher et al. 2015). Systematic reviews have failed to identify sufficient high-quality evidence supporting pulmonary rehabilitation as a treatment that has a large effect on balance measures in COPD (Hakamy, Bolton & McKeever 2017; Puhan et al. 2016). However, randomised control trials have indicated that specific balance components integrated into pulmonary rehabilitation are able to improve measures of balance in COPD (Beauchamp et al. 2013; Hill 2014; Marques et al. 2015; Mkacher et al. 2015).

Participation in generalised pulmonary rehabilitation may have a small impact on balance control (Beauchamp et al. 2010; Pichon et al. 2012), whereas specific balance training as a treatment arm of conventional pulmonary rehabilitation may have a more substantial impact on improving balance in COPD (Mkacher et al. 2015). A randomised control trial of COPD participants in either standard pulmonary rehabilitation or standard pulmonary rehabilitation with an additional three times a week balance training intervention found the control group to improve in TUG tests and ABC scale, and Unipodal Stance Test (UST) scores improved ($p= \leq .05$) (Mkacher et al. 2015). Interestingly, a larger treatment effect was evident in the intervention group than the control group in the TUG, ABC, UST, Tinetti, and BBS scores ($p= \leq .05$) (Mkacher et al. 2015). A similar study of balance adaptations after 6 weeks of balance training concurrent to standard pulmonary rehabilitation found high compliance with the additional training (82.5%) with no adverse effects and a statistically significant improvement in BBS ($p= .01$), BESTest ($p= .01$), and the 30-second chair-stand test scores ($p= .02$) (Beauchamp et al. 2013).

Pulmonary rehabilitation programs often have a broad-brush approach to inclusion criteria and treatment aims, meaning people with COPD are not typically screened for balance impairment. Individually tailored therapy programs could result in more effective treatment. A study of 36 adults with stable COPD and inclusion criteria of decline in balance, fall or near-fall were randomised to either standard pulmonary rehabilitation or standard treatment combined with balance-specific training (intervention group) (Hill 2014). The intervention group received additional stance exercises, transition exercises, gait exercises and functional strengthening with increasing difficulty, and they produced statistically significant improvements in BBS (5.4 units; 95%CI: 2.1 to 8.6) and BESTest scores (9.6 units; 95%CI: 3.9 to 15.3) compared to controls (Hill 2014). There are few other studies available to corroborate and expand understanding of these results.

Exertional walking tests for pulmonary rehabilitation in COPD

Exercise testing is a fundamental component of COPD assessment to determine individual treatment needs, stratify disease severity, ascertain baseline level of physical function (Ho & Maa 2016), and establish the effect of participation in exercise interventions (Jenkins 2007). The 6MWT and ISWT are two field tests commonly utilised to determine appropriate levels of training intensity and for prognostication in COPD (Ho & Maa 2016). The Global Strategy for the Diagnosis, Management, and Prevention of COPD recommend that field walking tests such as the 6MWT and the ISWT be assessed regularly to establish disease severity, measure the effect of participation in pulmonary rehabilitation, and monitor for a reduction in exercise capacity (Mirza et al. 2018).

The physiological response to the 6MWT and ISWT is similar when comparing end-test changes in cardiorespiratory measures but have different intra-tests profiles because of the different implementation methods (Holland et al. 2014). The 6MWT is self-paced and has steady-state oxygen uptake after the third minute, whereas the ISWT is externally-paced, and due to the incremental nature, has a more rapid rise in oxygen uptake (Holland et al. 2014). A technical standards document adapted from Holland et al. (2014) on standards for field tests for chronic obstructive respiratory disease state the 6MWT and the ISWT:

- have good test-retest reliability (Singh et al. 2014);

- are responsive to treatment effects (McCarthy et al. 2015);
- can elicit similar peak oxygen uptake to values experienced during a cardiopulmonary exercise test (Hill et al. 2012);
- are sensitive to variations in test conditions such as encouragement (Guyatt et al. 1984), and other test variations; and
- have an identifiable minimal important difference value (30 m for 6MWT distance and 10 m for the ISWT) (Holland et al. 2014).

Unknown impact of exertion on walking stability

Exertional walking tests have been used in clinical practice in the COPD population for decades and appear to be safe clinical tests that safely and effectively evoke exertion without placing people at undue risk of falling. Despite prevalent use of the 6MWT and ISWT there are few studies available that advise on safe exertional parameters during testing or even identify frequency of observed adverse events during testing. An exception to this trend is a study designed to identify the type and frequency of adverse events recorded during the 6MWT, a study of 741 people attending pulmonary rehabilitation were recruited (Jenkins & Čečins 2011). The study identified one event of chest pain, one event of tachycardia, and 35 events of oxygen desaturation below 80%, but no fall events or near-miss falls were recorded (Jenkins & Čečins 2011). Another example is a retrospective audit conducted to determine if adverse events are associated with desaturation below 80% (during the 6MWT) which found 11% desaturated below SpO_2 80% intra-walk test but not one of the participants recorded an adverse event associated with loss of postural control or falling (Afzal et al. 2018). Although loss of postural control, poor walking stability, or accidental falls are not reported as adverse events that occur commonly during exertional walk tests (Afzal et al. 2018; Jenkins & Čečins 2011) the ability to identify subtle changes in gait and balance in response to increased exertion is of clinical significance as it is unknown if there is a threshold point at which increased exertion places people at greater risk of falling.

Exertional walking tests are reported to be safe when monitored, however there is a sparsity of studies that directly investigate the impact that increased exertion has on gait stability or postural control. Consequently, it is unsubstantiated if effortful walking tests increase the risk of falling during or immediately post-test. Gait variability measures are commonly taken at comfortable walking speeds or use normalised velocity. This practice of gait assessment may not be sensitive to changes in gait variation (or postural control) resulting from increasing walking speeds and subsequent increased exertion or fatigue.

CHAPTER 3

Methods

Trial registration

Australia New Zealand Clinical Trials Registry Number: 12616000030471,

submitted 14/1/2016; Approved 18/1/2016.

Tasmanian Health and Medical Human Research Ethics Committee Approval Number: H0015372,

submitted: 06/11/2015; Approved: 17/12/2015

Aims

To determine the effect of exertional walking on gait regularity and dynamic balance in adults with Chronic Obstructive Pulmonary Disease (COPD).

Hypotheses

Hypothesis 1

In people with COPD, increased exertion during walking tasks decreases gait regularity and immediately after exertional walking dynamic balance is reduced.

Hypothesis 2

There is an identifiable relationship between the level of exertion during walking and changes in gait regularity in people with COPD.

Study Design

The study design is a randomised crossover trial conducted with 20 individuals who have COPD and attend pulmonary rehabilitation. Two exertional walking tasks are required to enable a comparison between a submaximal (internally paced) walking task and a maximal (externally-paced) walking task.

The Six-Minute Walk Test (6MWT) is commonly used in clinical assessment because it is time-limited, self-paced, and submaximal. A submaximal walking task will help determine if people can internally govern their own level of exertion effectively to maintain a consistent walking pattern. The Incremental Shuttle Walk Test (ISWT) is externally-paced, has set incremental velocities, and is conducted to volitional fatigue. Utilising this test may identify a threshold at which increased exertion produces a change in gait regularity. Walking speeds set to externally-paced velocities are likely to minimise the impact of motivational variation and fluctuations in exertion. Including both tests in a crossover design enables comparison between self-paced and externally-paced walking patterns while simultaneously comparing the level of exertion to walking pattern consistency.

Data collection occurred over three visits (Table 3.1). Participants attended on visit number one to provide participant descriptive measurements (as described under 'measures'), have their height and weight recorded, and undergo lung function testing. During visit number two and three, the allocated walking task was completed initially, and then again after a thirty-minute rest. Gait variability, exertion, and perceived level of exertion were measured concurrently during each walking task. Dynamic balance was tested before and after each exertional walking task.

Visit:		**1**		**2**		**3**
Event:	Recruitment	Information session and participant consent	Randomisation	First allocated Walk task (6MWT or ISWT)	Crossover and 1-week rest	Second allocated walk task (6MWT or ISWT)
				Outcome measurement		
				Participant initiated physical activity monitoring, eating, and clothing standardisation prior to participation		

Table 3.1 Data collection overview timeline

Randomisation was conducted by a third researcher (not involved in data collection) and undertaken using computer software (Motulsky). Prior to attending visit number two, participants were randomly allocated to walking Task A (6MWT) or Task B (ISWT). At visit two, participants completed one of two walk tasks (either Task A or Task B) and then completed the alternative walking task one week later, during the third and final visit (Table 3.2).

Time (min):		**0–10**		**10–20**		**20–50**		**50–60**	
Event:	Limited Exertion for 48 hours prior to assessment	Induction and orientation	Baseline RPE and FR	Initial 6MWT or ISWT	Finish RPE and FR	Rest period (30 min)	Baseline RPE and FR	Repeat 6MWT or ISWT	Finish RPE and FR
			Concurrent to the walking task: 1. Gait variability is recorded using a gate sensor mat 2. Exertion is recorded using pulse oximetry and a capnograph				Concurrent to the walking task: 1. Gait variability is recorded using a gate sensor mat 2. Exertion is recorded using pulse oximetry and a capnograph		

RPE= Rate of Perceived Exertion; FR= Functional Reach

Table 3.2 Assessment session timeline

To minimise the risk of harm, the exertional walking task could be self-terminated if the participant felt they were no longer able to participate in the assessment. The walking task could also be ended at the determination of the data collector (a registered Physiotherapist). Reasons for termination include a near-miss fall, an unsafe or increasingly unstable gait, a change in observational measures of exertion outside of acceptable levels, or a change in the level of cognition of the participant. All uncompleted assessments were accompanied by a description of why the test was terminated.

Setting

The study was conducted at the University of Tasmania Exercise Physiology Clinic located on the Newnham Campus in Northern Tasmania, Australia. Participants in the study were recruited from Pulmonary Rehabilitation Groups operating at the same venue. Data collection occurred at this site to ensure participants had accessibility to the venue and to utilise equipment available in the controlled environment of the Exercise Physiology Clinic. The study was carried out under the supervision of a Physiotherapist, an Exercise Physiologist, and an assistant, to ensure adequate supervision, and for maintenance of data integrity.

Participants

Participants were comprised of current or recent attendees of Pulmonary Rehabilitation (at the University of Tasmania, Newnham Campus). Only adults (over the age of 18 years) with a confirmed diagnosis of COPD (and GOLD classification using spirometry) were included in the study. Participants must be able to provide informed consent to participate in the study, ambulate independently on a flat even surface (to complete the test safely), and live at home (with or without oxygen supplementation).

People excluded from the study were those who have end-stage COPD requiring palliative management, or people with a self-reported acute infective exacerbation in their symptoms. People that require a gait aid, a prosthetic limb, or physical assistance to walk were also excluded from the study to enable clean data capture on a gait sensor mat and reduce the interference of a gait aid augmenting gait stability. Other exclusions include people with a significant neurological condition affecting their gait regularity, and pregnant females.

Sample size and justification

As this is the first study to examine changes in gait variability and balance during exertional tasks in people with COPD, a clinically relevant sample size of 20 had been selected. We have not been able to identify any literature reporting changes in gait variability and balance during exertional tasks in any other clinical or non-clinical population. Therefore, this project is pilot work to determine the feasibility and number of participants required for a larger comparative study.

Recruitment

Recruitment targeted participants of the Pulmonary Rehabilitation program operating at the University of Tasmania (Newnham Campus) using a recruitment poster. The poster had an invitation to participate in the study, outlined what the study involved, and offered an invitation to attend an information session. Those expressing an interest to attend the information session recorded their contact details on a sign-up sheet or contacted the researcher directly to have their enrolment recorded.

People attending the information session received a participant information sheet. During the information session, the researcher (who was not their treating clinician) outlined the procedure involved in the study, explained the inclusion and exclusion criteria, and invited those consenting to be involved in the study to indicate their informed consent by signing a consent form. Participants were informed that they would not be disadvantaged if they chose not to participate in the study.

Measures

Participant descriptive data was collected in an interview and included Sex, date of birth, length of time from diagnosis of COPD, relevant past medical history, smoking history, medications (including supplementary oxygen), and self-reported weekly activity habits.

Height and weight measurements were taken using a wall-mounted tape measure and floor scales. A lung function test was taken using a spirometer (COSMED Pony FX). Spirometry measures included: Forced Vital Capacity (FVC) – the total volume of air that the patient can forcibly exhale in one breath; Forced Expiratory Volume in 1 second (FEV_1) – the volume of air that the patient can exhale in the first second of forced expiration; and the ratio of FEV_1 to FVC (FEV_1/FVC). This data can be compared to normative data and be used to calculate COPD severity using the Global Initiative for Chronic Obstructive Lung Disease Spirometry Criteria for COPD (Vestbo et al. 2013). During

Spirometry testing, participants were instructed to take a breath-in until the lungs feel full, hold their breath long enough to seal their lips tightly around the mouthpiece, then blast the air out as forcibly and fast as possible until there is no more air left.

Two validated tools for measuring exertional walking were utilised, the 6MWT and the ISWT. The 6MWT is a submaximal test with normative data developed for community-dwelling older adults (Steffen, Hacker & Mollinger 2002) and it is used as a performance measure of gait endurance (Guyatt et al. 1985). Two tests within 30 minutes are required for validity. The object of this test is to walk as quickly as possible for six minutes between two markers, so that the participant can cover as much ground as possible. The participant may slow down if necessary or stop. The participant may recommence walking again as soon as possible, until the full six-minute duration has elapsed.

The ISWT is a standardised externally-paced incremental field walking task that provokes a symptom-limited maximal performance (Singh et al. 1992). It is used to assess functional capacity in people with chronic airways obstruction. One test is required for learning; a repeat test is then performed for assessment. The participant is required to walk between two cones, set nine metres apart, in time to a set of auditory beeps played on a CD. Initially, the walking speed is very slow, but each minute the required walking speed progressively increases. The participant walks until they are either too breathless or can no longer keep up with the beeps, at which time the test ends.

Outcome Measures

Dynamic Balance is measured using Functional Reach Test (FR). FR test is a performance measure which identifies the ability to reach forward in bilateral stance (self-generated perturbation) (Duncan et al. 1990). The functional reach test can be performed quickly and safely and unlike other more robust measures of balance, in this context, can be applied to capture transient changes in balance control before elevated exertion levels return to baseline readings. This measure is performed before and after each intervention to identify a change in the dynamic balance after exertional walking. The participant is instructed to stand next to, but not touching, a wall and position the arm that is closer to the wall, at 90 degrees of shoulder flexion, with a closed fist. The assessor will record the starting position at the 3rd metacarpal head on the yardstick. The participant is then instructed to "reach as far as you can forward without taking a step." The finishing position of the third metacarpal is then recorded. Scores are determined by assessing the difference between the start and end position is the reach distance (cm).

Gait regularity is assessed on an 8-meter GAITRite mat using GAITRite analysis software (Manufactured by CIR Systems, Inc., 12 Cork Hill Road, Building #2, Franklin, NJ 07416, United States of America). GAITRite analysis is a valid and reliable tool for measuring selected spatial and temporal parameters of gait (McDonough et al. 2001).

Double support time, step length, and support base standard deviation were analysed for differences between the first two passes of the gait sensor when exertion levels are low, and the last two passes of the sensor mat when exertion levels are elevated. These gait variables are commonly used in gait assessment and are recognised as independent predictors of falls in older adults (Nantsupawat et al. 2015; Verghese et al. 2009). The standard deviation of stance time, stride time, and swing time are spatiotemporal gait measures with demonstrated ability to discriminate between fallers and non-fallers in both people with COPD and healthy older adults (Marques et al. 2017; Marques et al. 2018). Variability (using standard deviation) in these gait parameters was used to analyse change from the beginning to the end of the walk tests and observe change during the walk tests.

Physical exertion is measured using Heart Rate (HR), Respiratory Rate (RR), Peripheral Oxygen Saturation (SpO_2), and End-tidal Carbon Dioxide ($ETCO_2$) continuously during the walking tasks. These measures were collected using Capnography and Pulse Oximetry (data captured using a Nellcor™ N-85 handheld Capnograph/Pulse Oximeter calibrated and distributed by Medtronic Australasia Pty Ltd., 5 Alma Road, Macquarie Park NSW 2113, PO Box 945, North Ryde NSW 1670, Australia). A Pulse Oximeter is a non-invasive lightweight device that clips onto the finger and displays the calculated oxygen saturation percentage, and will display heart rate (DeMeulenaere 2007). Capnography is a non-invasive method of monitoring respiration and can be used to record RR and $ETCO_2$ levels (Casey 2015).

Perceived exertion is recorded using the Modified Borg Dyspnoea Scale. The dyspnoea scale is a 10-point self-rated perception of shortness of breath commonly used during the 6MWT as an indicator of exertion (Ries 2005). The Modified Borg Dyspnoea Scale measure is taken before the task, at 30-second intervals during the task, and on completion of each exertional task.

Data Collection and Analysis

A Consort Flow Diagram is utilised to standardise data collection processes. Numbers of potential participants screened and those who meet the inclusion criteria were recorded, with any excluded participants along with the reasons for exclusion recorded using the consort flow diagram (Figure 3.3).

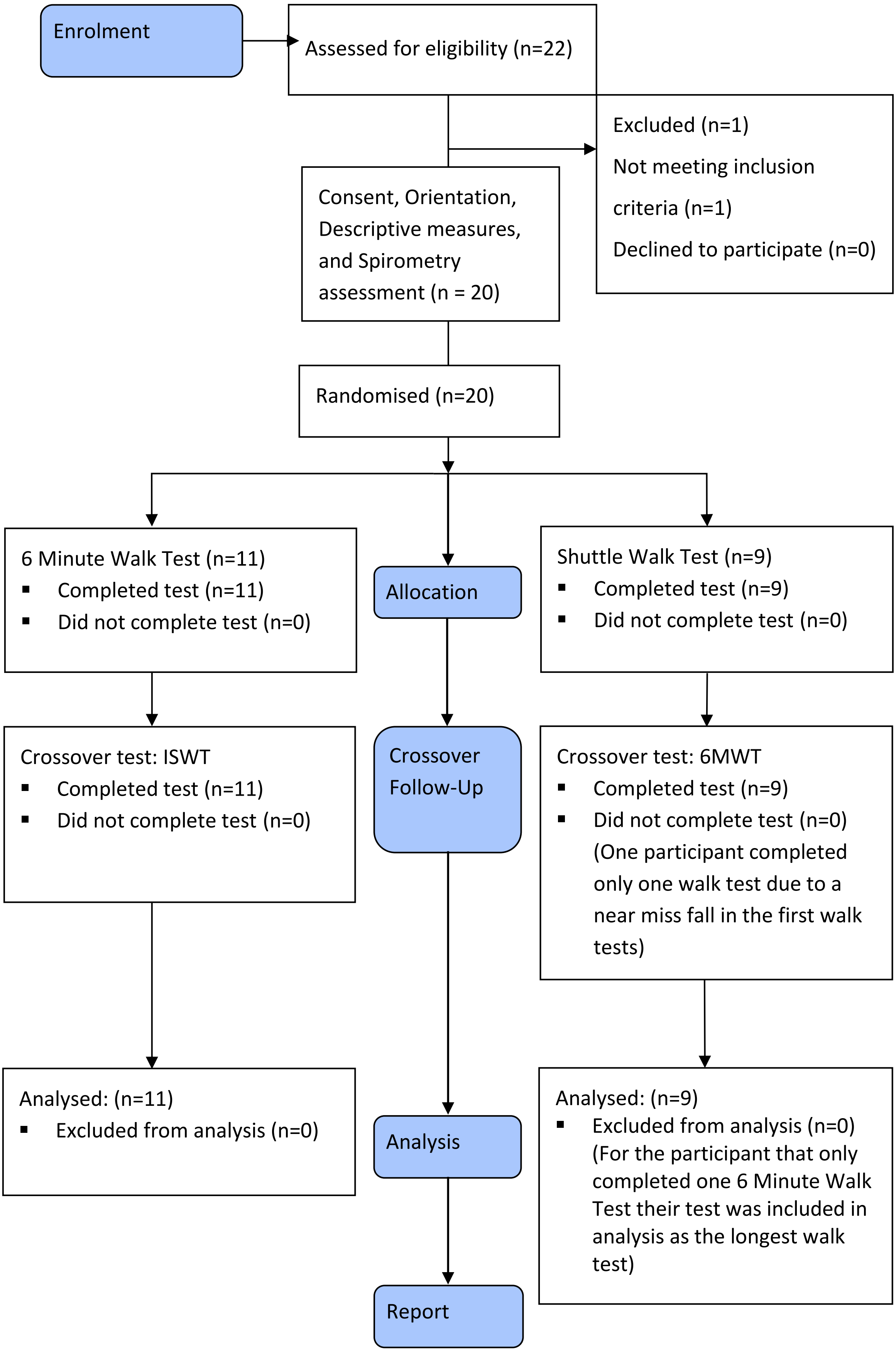


Figure 3.1 Study rationale and design consort flow diagram

Data collection was undertaken with a minimum of two trained supervisors to ensure the safety of the people participating in the study and adherence to data collection protocol. Standardisation of assessment processes to ensure inter-test assessment reliability included the correct application of standardised tests and consistency of environment, e.g. shoes on or off, lead-in walking distance for capturing gait analysis. Additionally, tests for the same person were repeated near the same time of day between visit two and three, and activity levels and eating patterns prior to assessment were standardised and monitored. Deviations from the data collection process including adverse events or failure to complete the assessment were recorded and documented appropriately. Records were stored both in hard copy and electronically in a secure manner and retained securely for a standard period.

Data manipulation and statistical analyses

The impact of exertional walking on gait regularity is analysed using mixed-effects linear regression modelling for within-task and between task comparisons using R Studio, R version 3.3.3 (2017-03-06). Data was tested for normality in distribution and is presented as mean and standard deviation with 95% confidence intervals. Cohen's d statistic ('Statistical Power Analysis for the Behavioral-Sciences - Cohen,J' 1988) was used to analyse the effect size for the difference between the start-test and end-test means for gait variables. The effect size was categorised as small ($\leq .2$), medium (.2 to .5), or large ($\geq .8$).

Paired t-test between the start and end of exertional walking tests is used to assess the impact of exertional walking on gait variability and dynamic balance is measured by functional reach. Averages of the first two passes were taken as the 'start test' reading and the last two passes were taken as the 'end test' reading. Start and end-test comparisons are analysed in exertional walking stance time, swing time, double support time, step length, and support base standard deviation. FR was measured directly before (within 1 minute) and immediately (less than 30 seconds) following the exertional walk test.

Standard deviation is selected to measure variability of gait parameters as it is a common measure of fluctuations in stride to stride pattern, and stance time standard deviation has been demonstrated to have the greatest sensitivity and specificity to discriminate between fallers and non-falling older adults (Marques et al. 2017; Marques et al. 2018). Correlation coefficient using a Pearson's product-moment correlation (r value) with a corresponding p value and 95% confidence intervals is used to express the strength and direction of the linear relationship between the standard deviation of each gait variable and time, as well as for changes to gait regularity (stance, stride, and swing time standard deviation) and measures of exertion (rate of perceived exertion, oxygen saturation, end-tidal carbon dioxide level, respiratory rate, and heart rate).

CHAPTER 4

Results

Distribution of data

All data analysed were normally distributed and where appropriate is presented as mean and standard deviation.

Demographic Data

The number of participants was 20, comprising of 17 females and 3 males. Participant age ranged from 54 years to 83 years with a mean age of 70.8 (± 8.2) years (Table 4.1). Forced Expiratory Volume (FEV_1), Forced Vital Capacity (% FVC) mean was 63.7 (±17.5). The median Global Initiative for Chronic Obstructive Lung Disease (GOLD) ranking was 2 (Moderate). Of the participants, 3 had a GOLD ranking mild, 12 were moderate, 4 were severe, and 1 was very severe. The average Body Mass Index (BMI) was 28.0 (±5.2) kg/m^2. Polypharmacy was present in 65% of participants with the mean number of medications 7 (±7) (Table 4.1 and Table 4.2). Only one participant was on home oxygen and completed the walk test with oxygen running at 3 L/min (usual rate), using a portable oxygen concentrator unit and delivered via nasal prongs.

Table 4.1 Participant Demographics

Measure	n	Mean (SD)	Min	Max
Age (Years)	20	70.8 (±8.2)	54	83
FEV_1 (%FVC)	20	63.7 (±17.5)	26.1	92.1
GOLD Ranking	20	2.2 (±0.7)	1	4
BMI (kg/m2)	20	26.5 (±5.2)	17.3	38.2
Number of Medication/s	20	7 (±5)	0	18
Number of Respiratory infections / Year	20	1 (±1)	0	5
Number of Hospitalisations (last 12 months)	20	0 (±0)	0	1

Table 4.2 Polypharmacy (≥5 medications) Incidence and Home Oxygen use

	n	Yes (%)	No (%)
Polypharmacy	20	13 (65%)	7 (35%)
Home Oxygen	20	1 (5%)	19 (95%)

The mean number of passes completed in the 6MWT was 19 (±5) (Table 4.3). In the ISWT, the mean number of passes was 29.1 (±7) and the mean test conclusion time was 359.5 seconds (±68.94).

Table 4.3 Distance Covered in Walk Tests

Test	n	Measure	Mean (SD)	Min	Max
6MWT	19	Passes (25 m track)	19 (±5)	14	36
		Distance (m)	482 (±121)	350	900
		Time (sec)	360 (±0)	360	360
ISWT	20	Passes (10 m track)	29.1 (±7)	18	39
		Distance (m)	291 (±67)	180	390
		Time (sec)	359.5 (±68.94)	230	480

Adverse events

One participant completed both ISWTs but only one 6MWT. That person, under supervision, was observed to have a near miss fall (without injury) near the end of the first 6MWT, was deemed at risk of falling, and dissuaded from completing the repeat 6MWT. The participant was not on oxygen, was GOLD ranking 1, had not reported a falls history or recent acute exacerbation of COPD, and had a bronchiectasis type presentation of COPD. Data collected in that participant's first 6MWT was used in the data analysis. All other participants completed all the walk tests without adverse events.

Gait variability over time

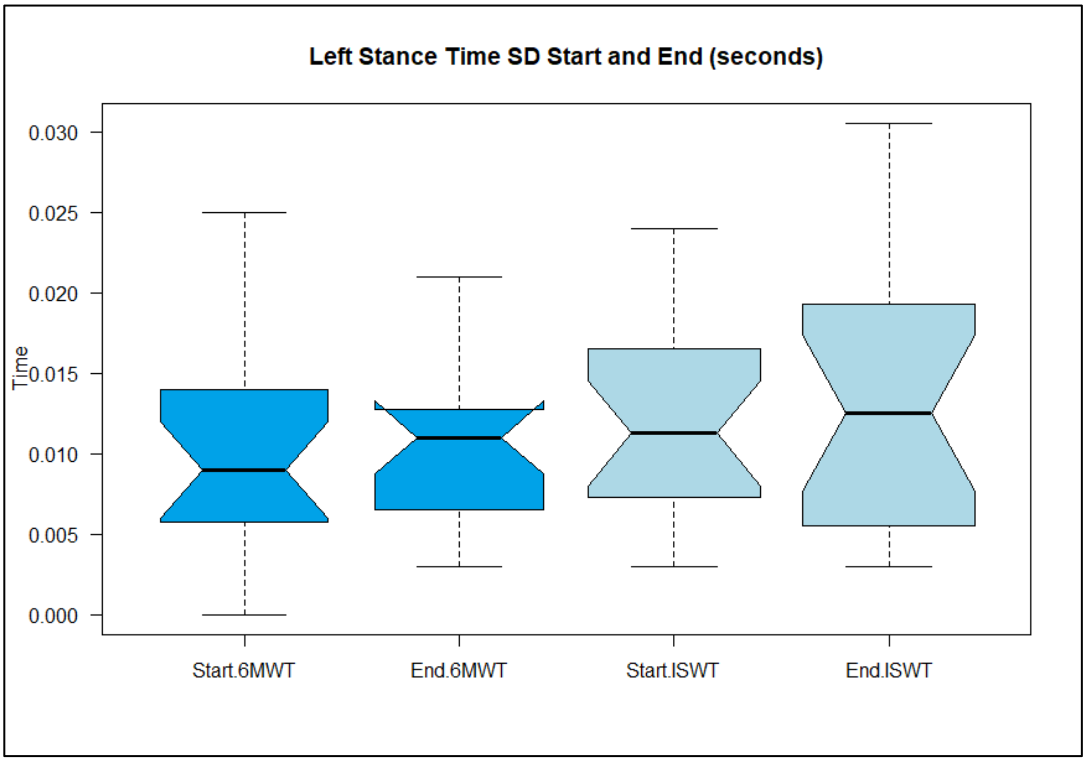
Gait variables were measured at the first two passes of the sensor mat (named start-test) and over the last two passes (named end-test), and throughout the walk tests at each pass of the gait mat.

Stance time standard deviation

Stance time is the duration (sec) one limb spends in contact with the ground from the heel first contacting the surface to the time the toes lift from the ground.

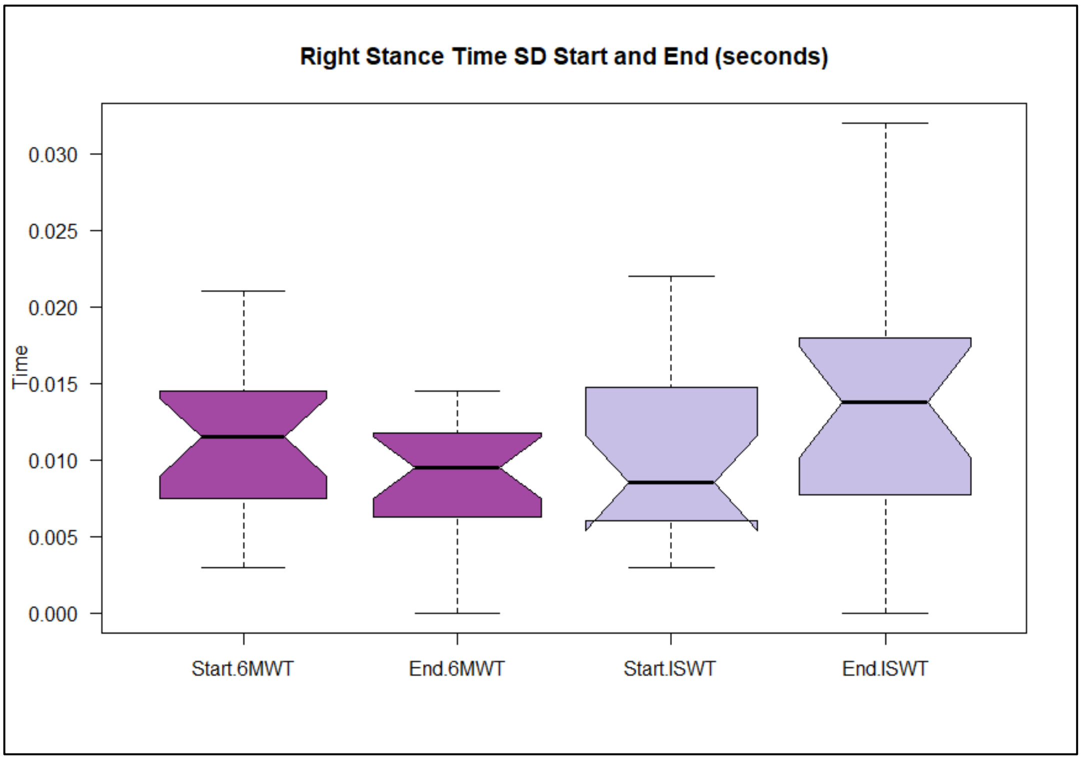
Stance time standard deviation in the 6MWT for the left side and right side had a start-test mean of 0.01 seconds (±0.01) and 0.01 (±0.01), respectively. Stance time standard deviation for the 6MWT measured at the last two passes of the sensor mat for the left side and right side was also 0.01 seconds (±0.01) and 0.01 (±0.01), respectively. A paired Cohen's d analysis showed a statistically small effect size in the stance time standard deviation from start to the end-test d= .06 (95%CI: .01 to .14) for the left side and d= .15 (95%CI: .07 to .22) on the right in the 6MWT. A paired t-test (two sided) analysis demonstrated no significant change from start to end-test stance time standard deviation in the 6MWT for the left p= .779 (95%CI: -0.003 to 0.003) or right p= .939 (95%CI: -0.003 to 0.003) (Figure 4.1a).

Stance time standard deviation in the ISWT had a start-test mean for the left and right of 0.01 seconds (±0.01) and 0.01 seconds (±0.01), respectively. End-test mean in stance time standard deviation for the ISWT left and right was 0.02 seconds (±0.02) and 0.01 (±0.01), respectively. In the ISMWT the effect size from the start to the end-test mean was statistically small with d= - .02 (95%CI: - .09 to .05) for the left and d= - .13 (95%CI: - .20 to - .06) on the right side. There was no significant change in ISWT start to end-test stance time standard deviation p= .398 (95%CI: -0.006 to 0.002) for the left, and p= .681 (95%CI: -0.004 to 0.005) on the right (Figure 4.1b).



Box and Whisker plot showing the interquartile distribution

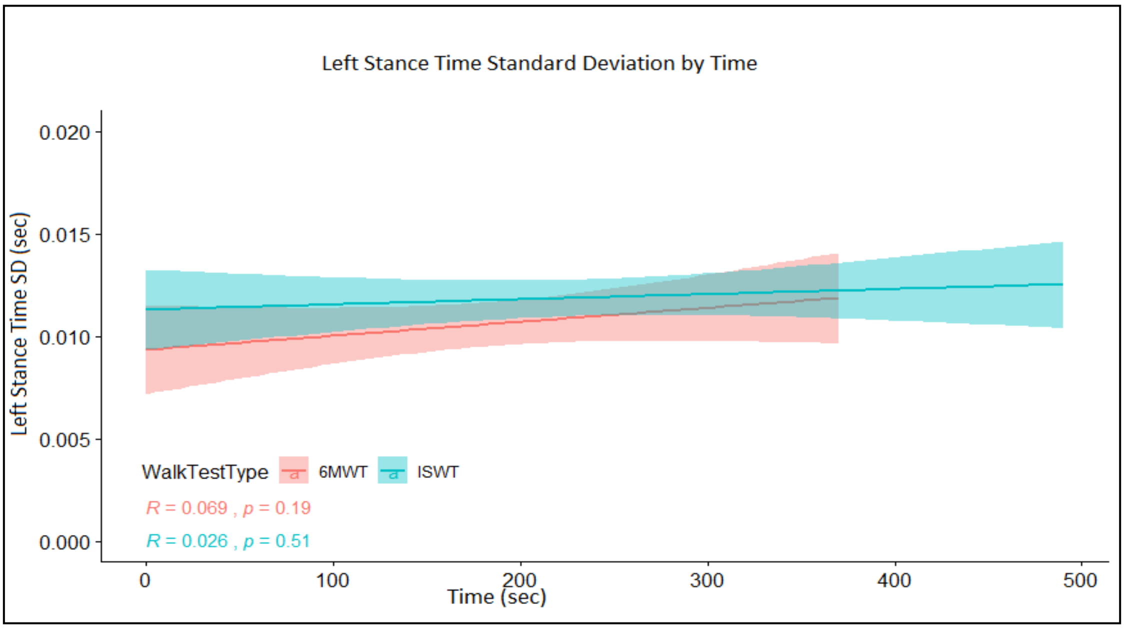
Figure 4.1a Left Stance Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT



Box and Whisker plot showing the interquartile distribution

Figure 4.1b Right Stance Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT

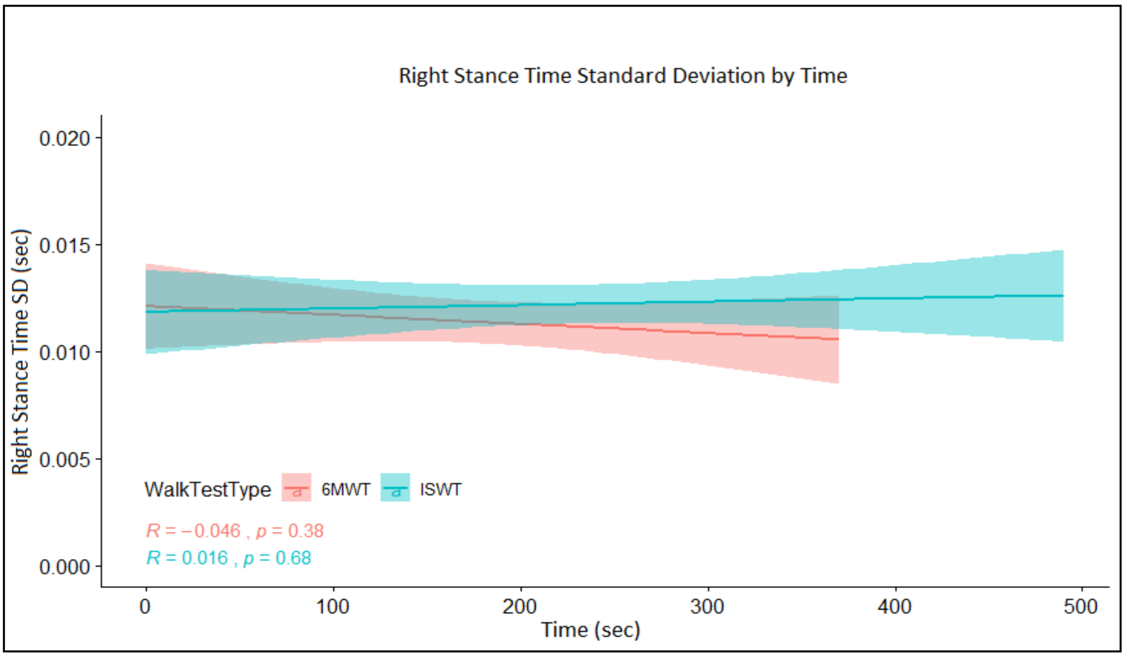
There was no association between left leg stance time standard deviation and time, for either the 6MWT (r= .069, p= .19) or the ISWT (r= .026, p= .51) (Figure 4.1c).



Linear regression plot displaying mean and 95%CI

Figure 4.1c Left Stance Time Standard Deviation Over Time

There was no association between right stance time standard deviation and time, for either the 6MWT (r= .046, p= .38) or the ISWT (r= .016, p= .68) (Figure 4.1d).



Linear regression plot displaying mean and 95% CI

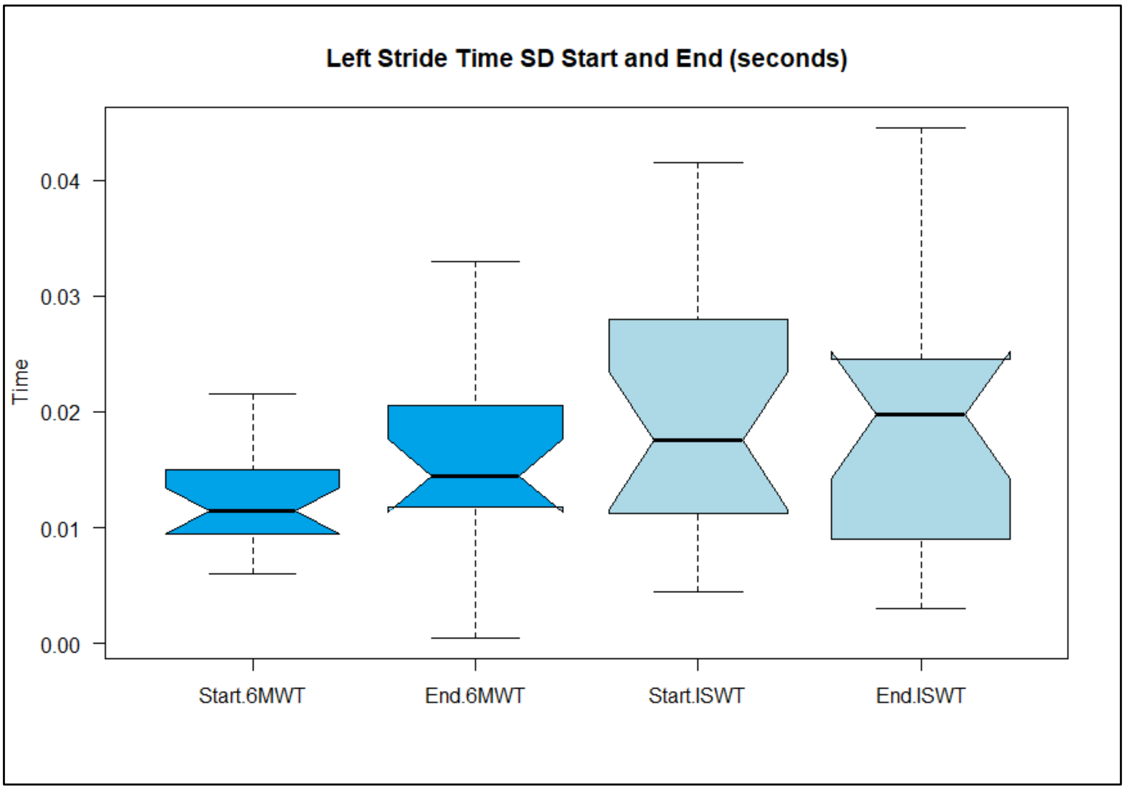
Figure 4.1d Right Stance Time Standard Deviation Over Time

Stride time standard deviation

Stride time is the duration between the first contact with the ground of two consecutive footsteps of the same foot.

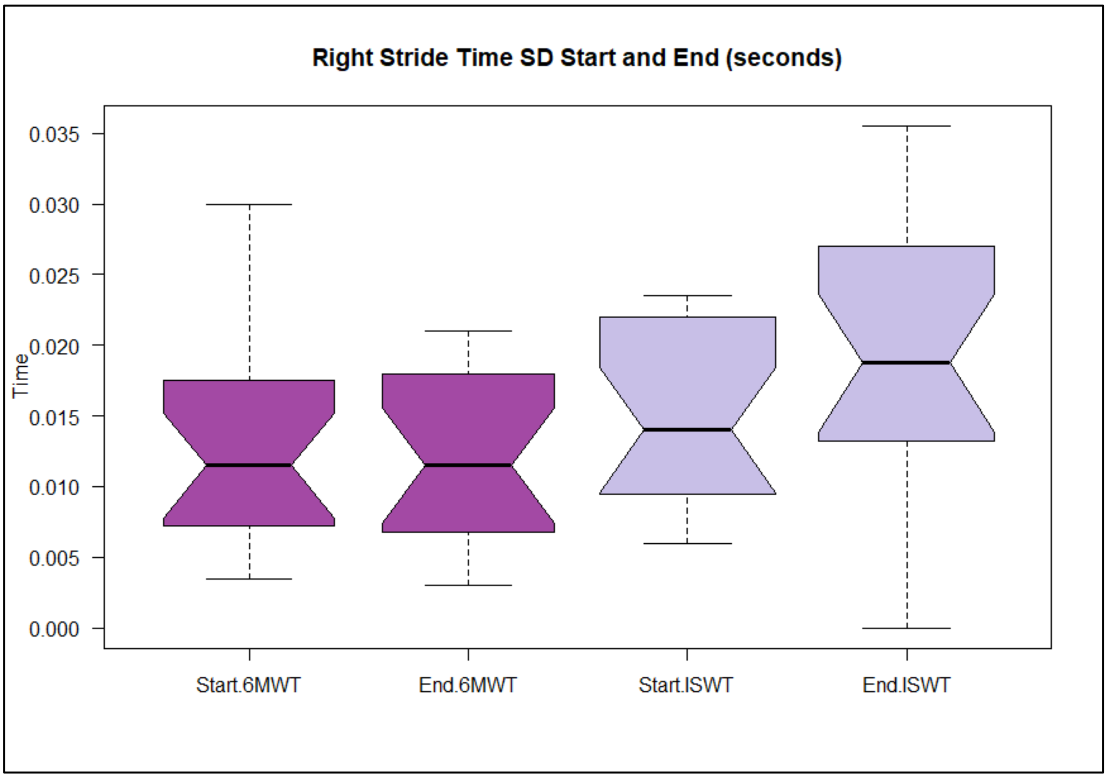
Stride time standard deviation in the 6MWT for the left and right side had a start-test mean of 0.01 seconds (±0.01) and 0.01 (±0.01), respectively. Stride time standard deviation for the 6MWT measured at the last two passes of the sensor mat for the left and right was 0.01 seconds (±0.01) and 0.02 (±0.01), respectively. Cohen's d analysis showed a statistically small effect size from the start to the end-test mean of d= .01 (95%CI: - .07 to .08) on the left side and d= .09 (95%CI: .02 to .16) on the right-side. A paired t-test (two sides) analysis demonstrated no significant change from start to end-test stride time standard deviation in the 6MWT for the left side p= .980 (95%CI: -0.003 to 0.003) or right-side p= .575 (95%CI: -0.006 to 0.003) (Figure 4.2a).

Stride time standard deviation in the ISWT had a start-test mean on the left and right side of 0.02 seconds (±0.01) and 0.01 (±0.01), respectively. End-test mean in stride time standard deviation for the ISWT on the left and right side was 0.02 seconds (±0.02) and 0.02 seconds (±0.01), respectively. A statistically small effect size of d= .07 (95%CI: .00 to .14) was observed on the left and d= - .07 (95%CI: - .14 to .00) on the right-side. There was no significant change in ISWT start to end-test stride time standard deviation p= .815 (95%CI: -0.004 to 0.003) for the left side, and p= .875 (95%CI: -0.005 to 0.006) on the right side (Figure 4.2b).



Box and Whisker plot showing the interquartile distribution

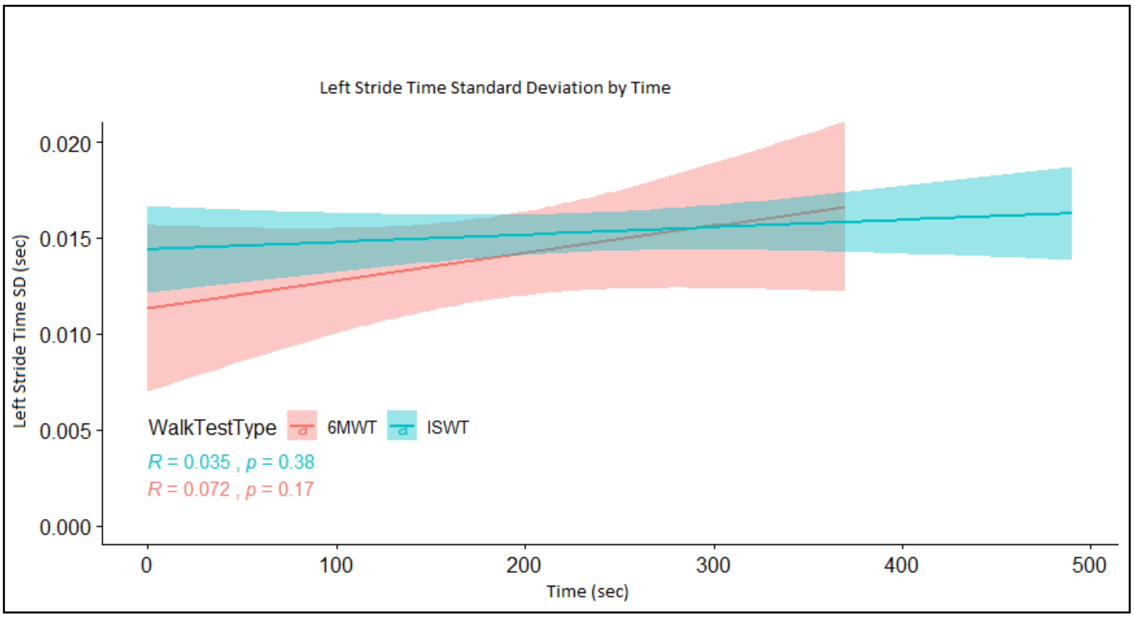
Figure 4.2a Left Stride Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT



Box and Whisker plot showing the interquartile distribution

Figure 4.2b Right Stride Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT

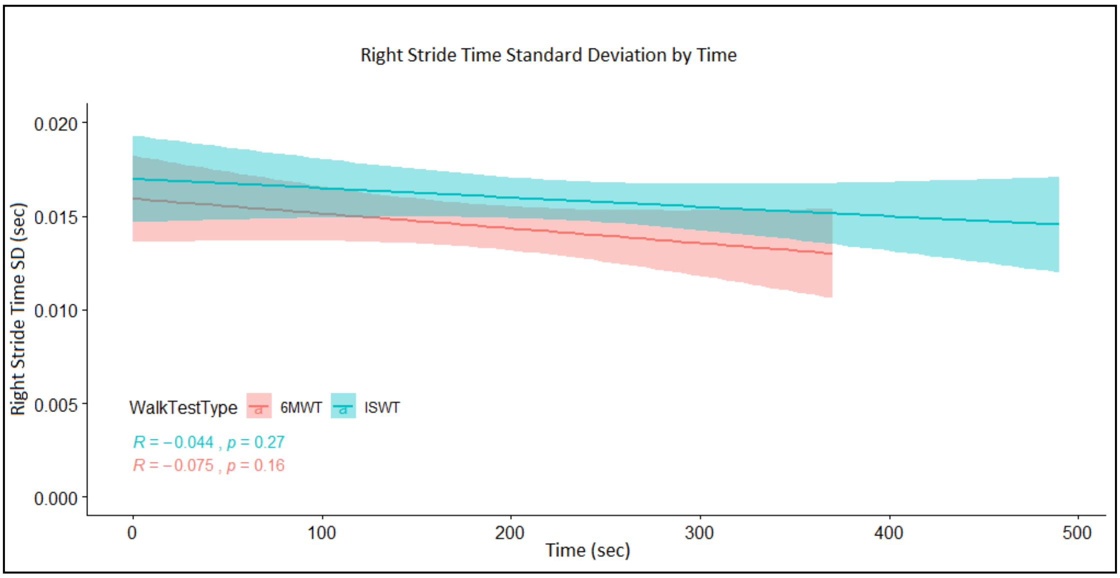
There was no association between left leg stride time standard deviation and time, for either the 6MWT (r= .072, p= .17) or the ISWT (r= .035, p= .38) (Figure 4.2c).



Linear regression displaying mean and 95% CI

Figure 4.2c Left Stride Time Standard Deviation Over Time

There was no association between gait variability measured as right stride time standard deviation and time, for either the 6MWT (r= .075, p= .16) or the ISWT (r= .044, p= .27) (Figure 4.2d).



Linear regression displaying mean and 95% CI

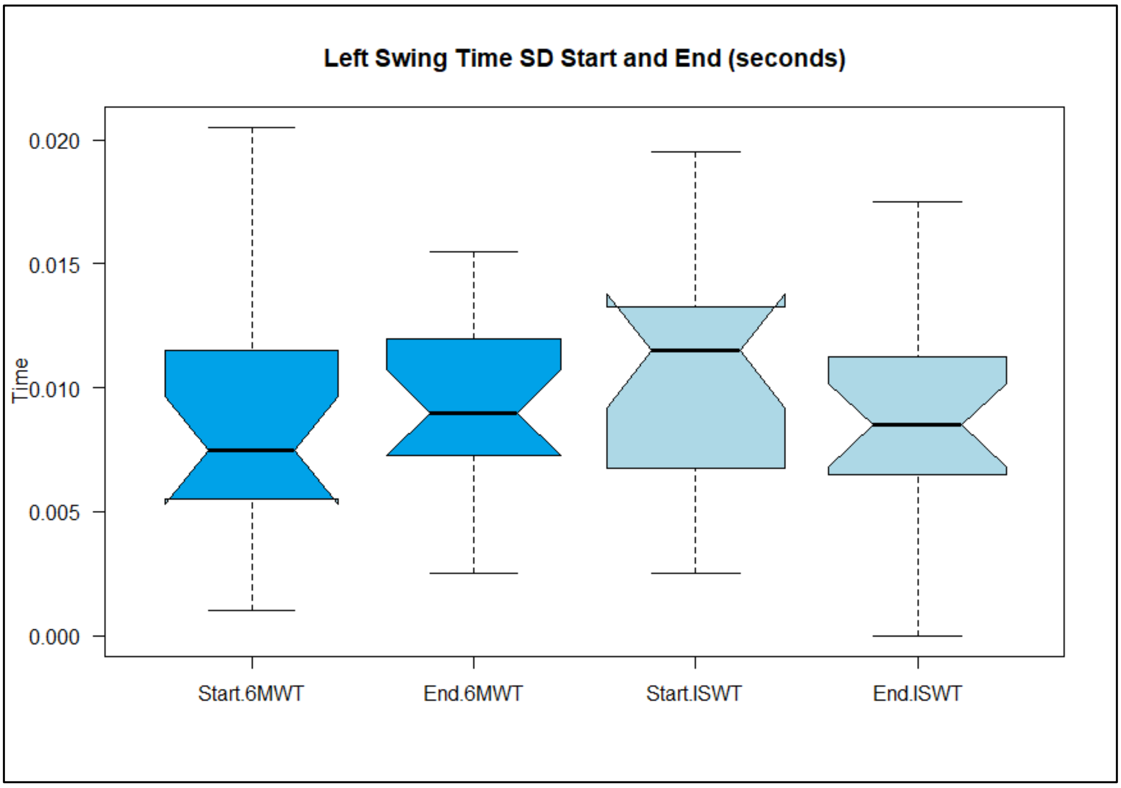
Figure 4.2d Right Stride Time Standard Deviation Over Time

Swing time standard deviation

Swing time is the duration in which the swinging foot is not in contact with the ground and is travelling from point of contact to point of contact.

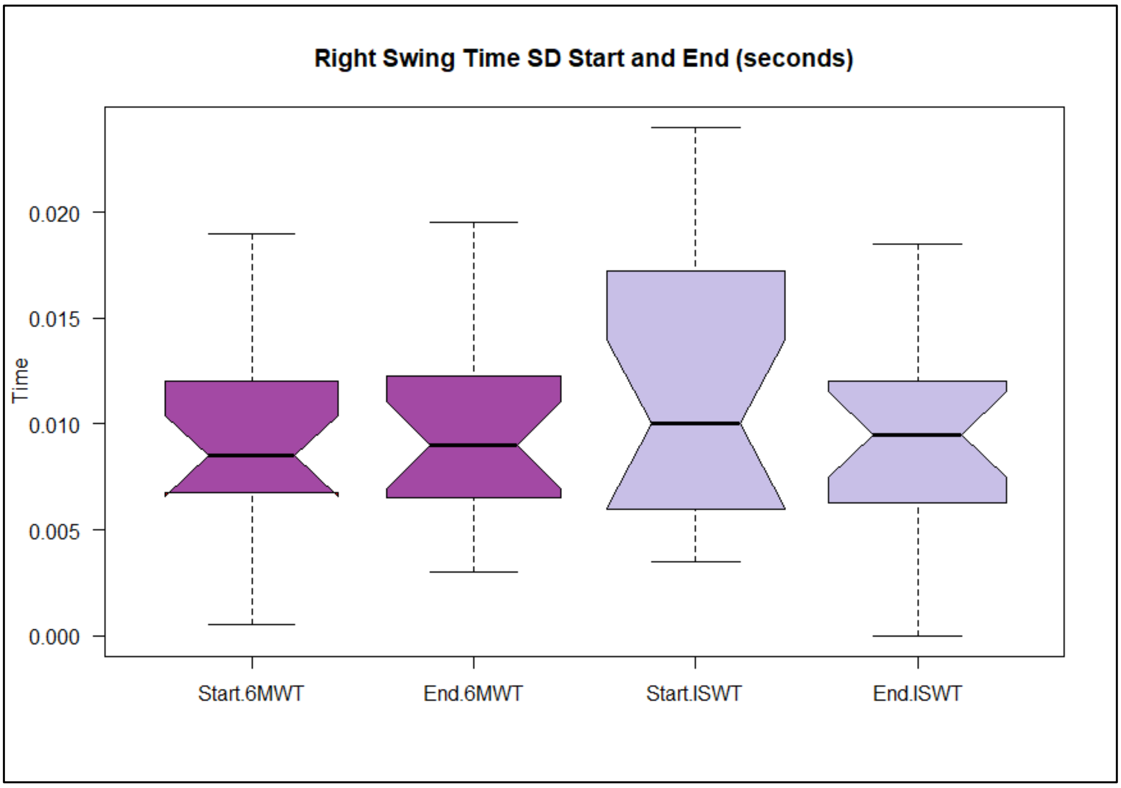
Swing time standard deviation in the 6MWT on the left and right side had a start-test mean of 0.01 seconds (±0.00) and 0.01 (±0.01), respectively. The mean swing time standard deviation for the 6MWT measured at the last two passes of the sensor mat for the left and right was 0.01 seconds (±0.00) and 0.01 (±0.01), respectively. Cohen's d analysis showed a statistically small effect size from the start to the end-test mean of d= .08 (95%CI: - .15 to - .01) on the left side but bordering on a moderate effect size of d= - .23 (95%CI: - .30 to - .15) on the right-side. A paired t-test (two sided) analysis demonstrated no significant change from start to end-test swing time standard deviation in the 6MWT on the left side p = 0.751 (95%CI: -0.002 to 0.002) or right-side p= .357 (95%CI: -0.001 to 0.003) (Figure 4.3a).

Swing time standard deviation in the ISWT had a start-test mean on the left and right side of 0.01 seconds (±0.01) and 0.01 (± 0.00), respectively. End-test mean in swing time standard deviation for the ISWT left and right side was 0.01 seconds (±0.00) and 0.01 (±0.00), respectively. A statistically small effect size of d= .09 (95%CI: .02 to .16) was observed on the left and right-side d= .03 (95%CI: -.04 to .10). There was no significant change in ISWT start to end-test swing time standard deviation p = 0.686 (95%CI: -0.002 to 0.001) for the left side, and p= .907 (95%CI, -0.002 to 0.002) on the right side (Figure 4.3b).



Box and Whisker plot showing the interquartile distribution

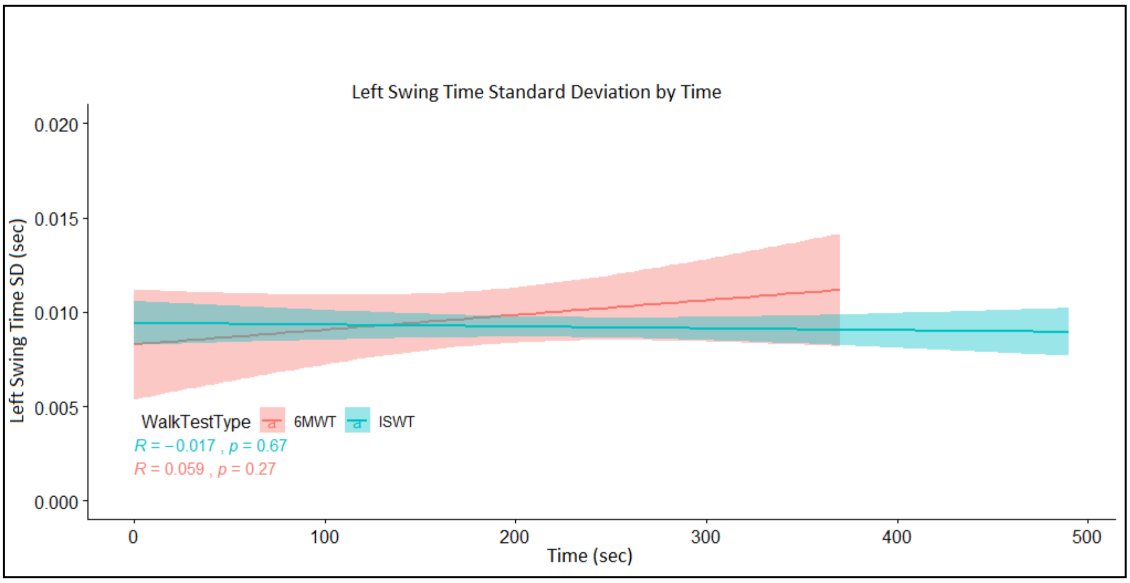
Figure 4.3a Left Swing Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT



Box and Whisker plot showing the interquartile distribution

Figure 4.3b Right Swing Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT

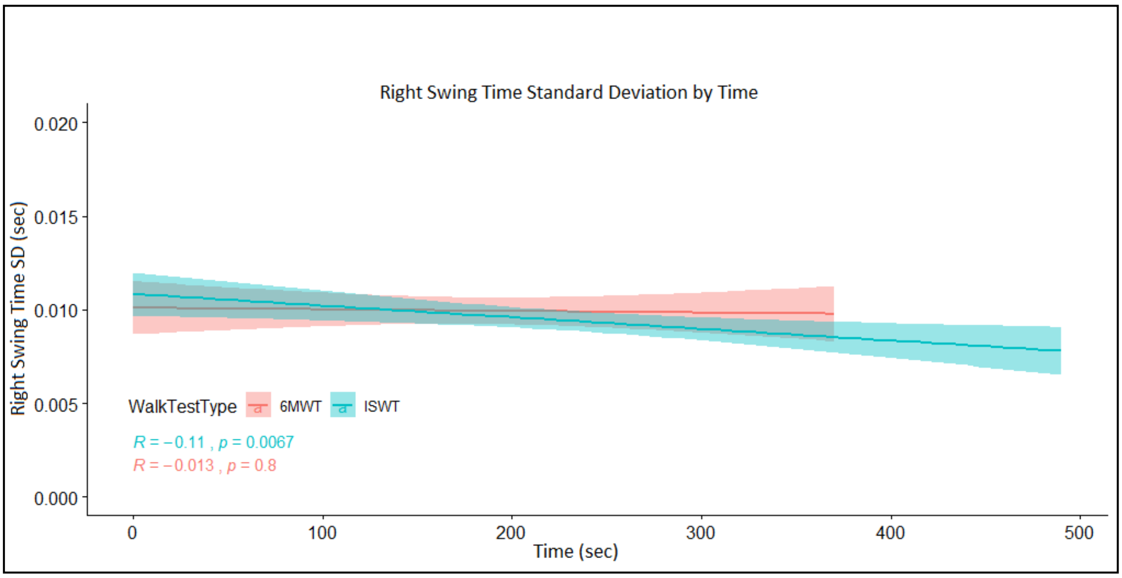
There was no association between gait variability measured as left leg swing time standard deviation and time, for either the 6MWT (r= .059, p= .27) or the ISWT (r= .017, p= .67) (Figure 4.3c).



Linear regression displaying mean and 95% CI

Figure 4.3c Left Swing Time Standard Deviation Over Time

There was a small but statistically significant association between right leg swing time standard deviation and time for the ISWT (r= .11, p= .0067) but not the 6MWT (r= .013, p= .8) (Figure 4.3d).



Linear regression displaying mean and 95% CI

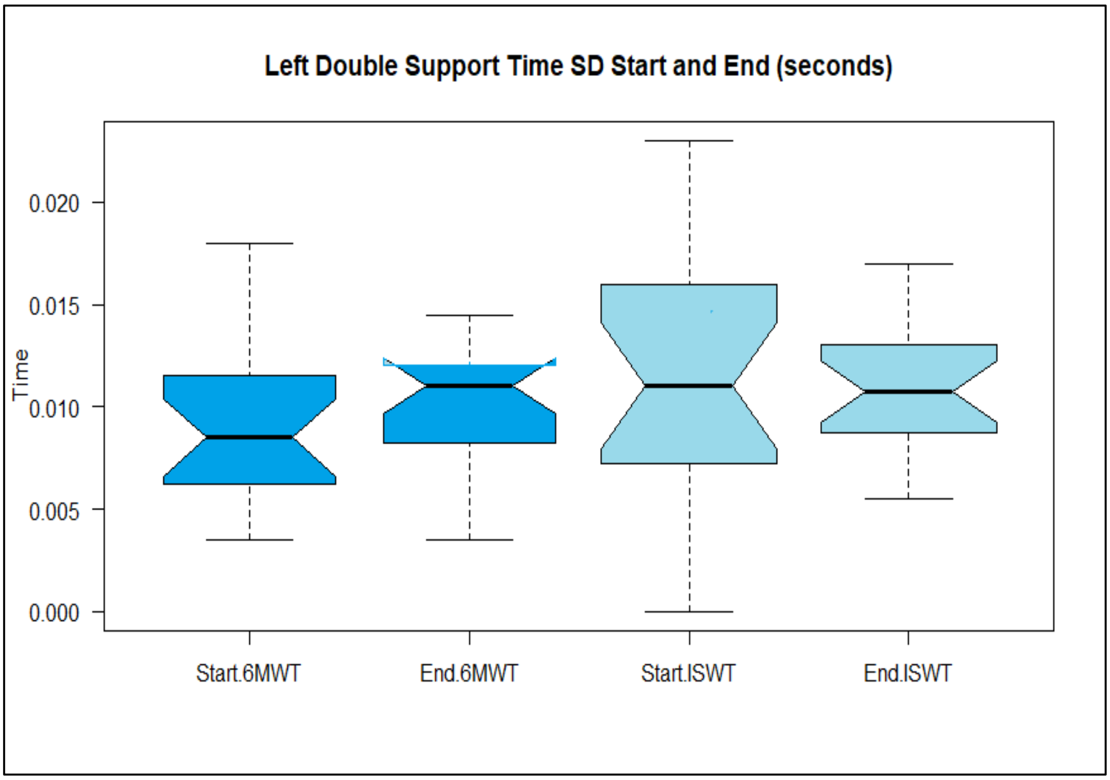
Figure 4.3d Right Swing Time Standard Deviation Over Time

Double support time standard deviation

Double support time is the duration of time both feet are in contact with the ground and was measured in seconds.

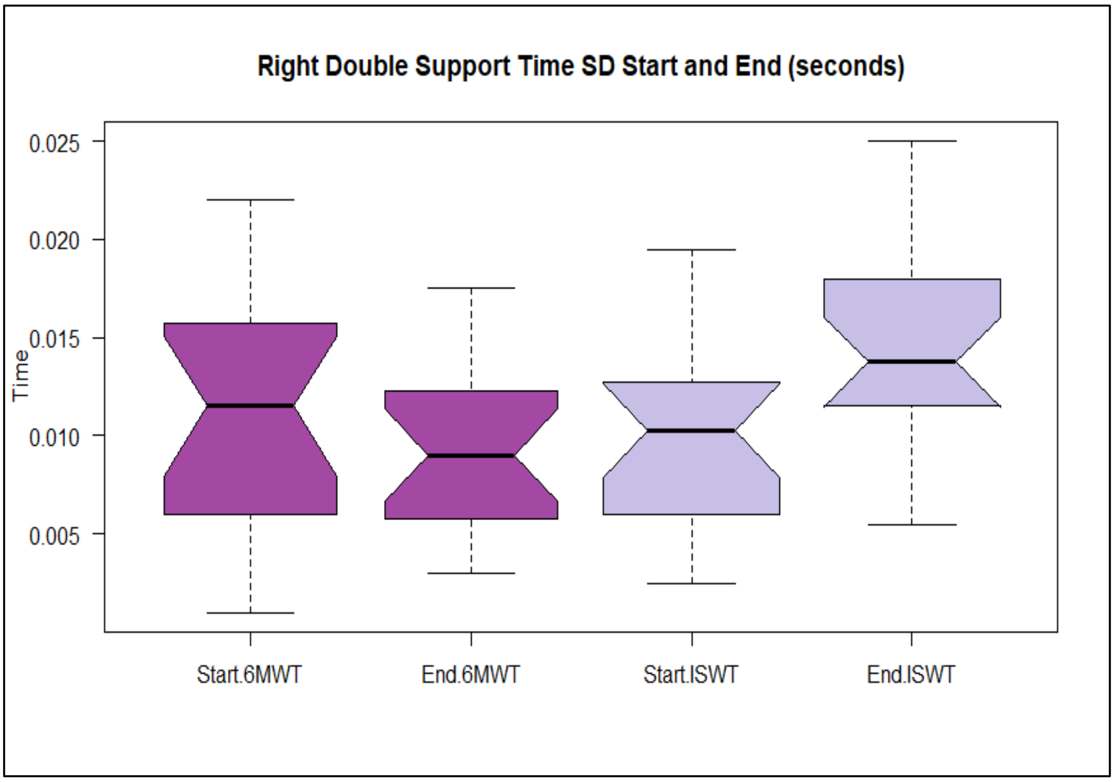
Double support time standard deviation in the 6MWT for the left and right side had a start-test mean of 0.01 seconds (±0.01) and 0.01 (±0.01), respectively. The mean of the last two passes of the sensor mat for the left and right side was 0.01 seconds (±0.00) and 0.01 (±0.00), respectively (Figure 4.4a). Cohen's d analysis showed a statistically small effect size from the start to the end-test mean of d= .05 (95%CI: - .02 to .12) on the left side but a moderate effect size of d= .30 (95%CI: .22 to .38) on the right-side. A paired t-test (two sided) analysis demonstrated no significant change from start to end-test double support time standard deviation in the 6MWT for the left side p= .797 (95%CI: -0.003 to 0.002) or right-side p= .097 (95%CI: -0.004 to 0.000).

Double support time standard deviation in the ISWT had a start-test mean for the left and right side of 0.01 seconds (±0.01) and 0.01 (±0.01), respectively. End-test mean in double support time standard deviation for the ISWT left and right side was 0.01 seconds (±0.00) and 0.02 (±0.01), respectively. A statistically small effect size of d= .00 (95%CI: - .07 to .07) was observed on the left and a borderline moderate effect size of d= - .20 (95%CI: - .27 to - .13) on the right-side. There was no significant change in ISWT start to end-test double support time standard deviation p= .995 (95%CI: -0.003 to 0.002) for the left side, and p= .552 (95%CI, -0.002 to 0.003) on the right side (Figure 4.4b).



Box and Whisker plot showing the interquartile distribution

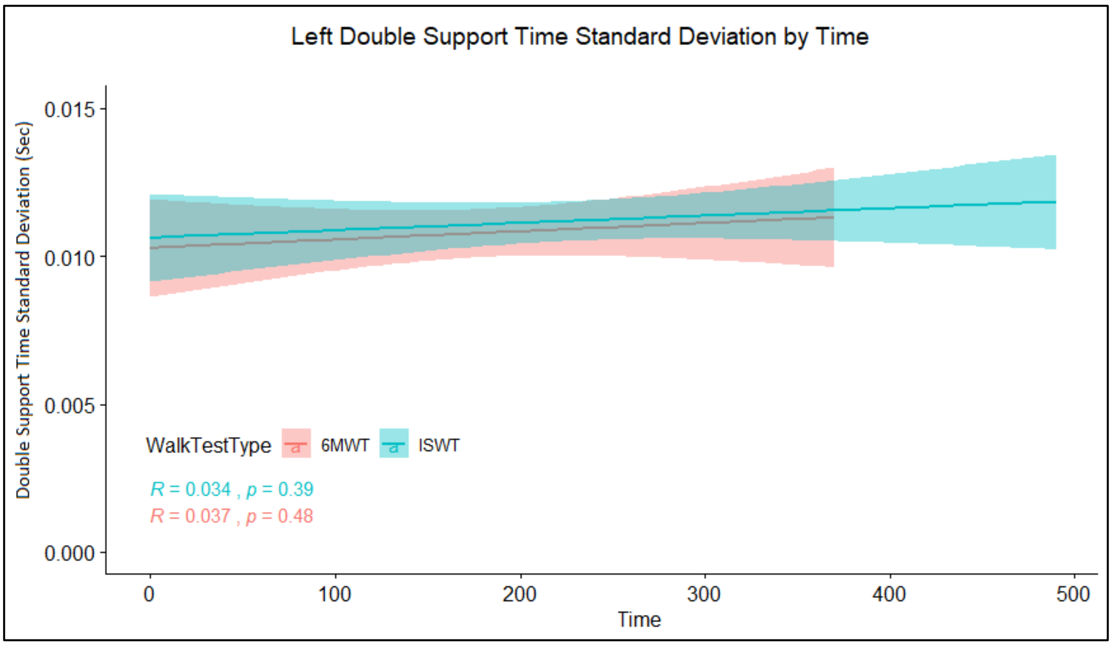
Figure 4.4a Left Double Support Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT



Box and Whisker plot showing the interquartile distribution

Figure 4.4b Right Double Support Time Standard Deviation (seconds) at Start and End-test for 6MWT and ISWT

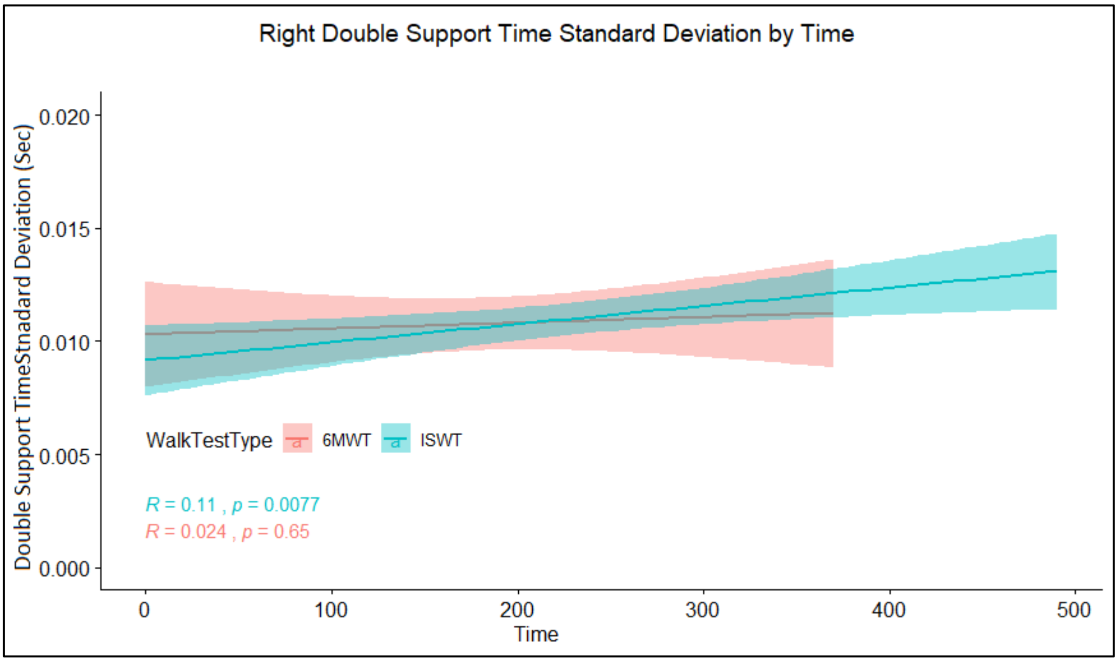
There was no association between left leg double support time standard deviation and time, for either the 6MWT (r= .037, p= .48) or the ISWT (r= .034, p= .39) (Figure 4.4c).



Linear regression displaying mean and 95% CI

Figure 4.4c Left Double Support Time Standard Deviation Over Time

There was a small but statistically significant association between right-side double support time standard deviation and time for the ISWT (r= .11, p= .0077) but not the 6MWT (r= .024, p= .65) (Figure 4.4d).



Linear regression displaying mean and 95% CI

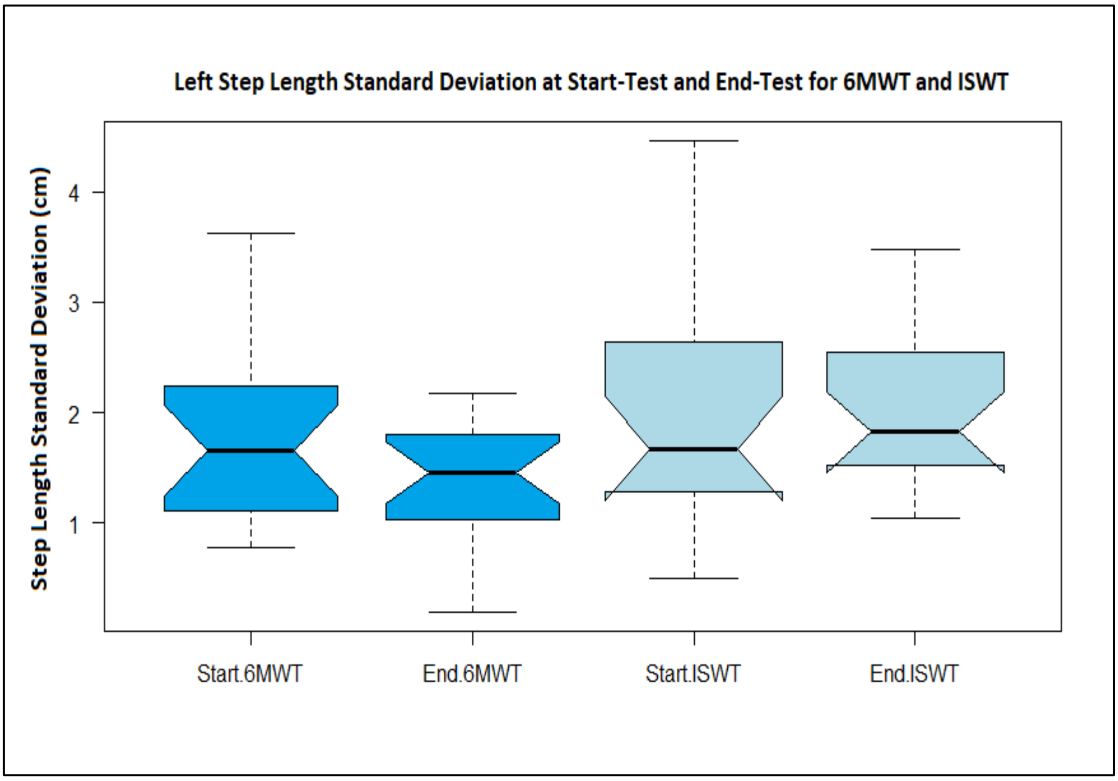
Figure 4.4d Right Double Support Time Standard Deviation Over Time

Step length standard deviation

Step length is the longitudinal distance from the heel contacting with the ground of one foot to the heel contacting the ground in the alternate foot.

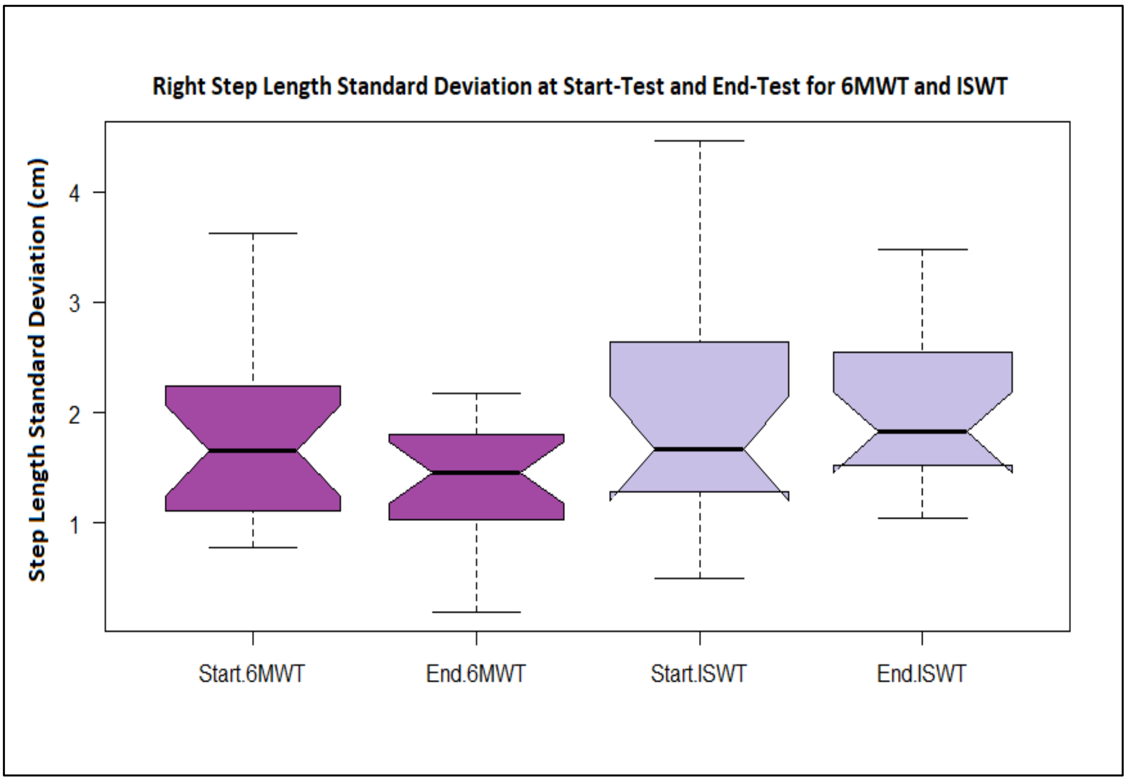
In the 6MWT for the left side, there was no statistically significant change in the step length standard deviation from the start-test mean of 1.93 (±1.09) to the end-test mean of 1.40 cm (±0.73) p= .960 (95%CI, -0.353 to 0.335) (Figure 4.5a). Similarly, there was no statistically significant change for the right-side step length standard deviation from start-test mean 1.63 cm (±1.07) to end-test mean 1.44 cm (±0.91) p= .421 (95%CI: -0.492 to 0.207) (Figure 4.5b). Cohen's d analysis showed a statistically small effect size from the start to the end-test mean of d= .01 (95%CI: - .06 to .08) on the left side and d= .18 (95%CI: .11 to .26) on the right-side.

In the ISWT for the left side, there was no statistically significant change in the step length standard deviation from the start-test mean of 1.98 (±1.04) cm to the end-test mean of 2.01 cm (±0.70) p= .307 (95%CI: -0.159 to 0.501) (Figure 4.5a). Similarly, there was no statistically significant change for the right-side step length standard deviation from start-test mean of 1.73 cm (±1.07) to end-test 2.14 cm (± 1.06) (p= .949; 95%CI: -0.348 to 0.326) (Figure 4.5b). A statistically borderline but moderate effect size of d= - .25 (95%CI: - .33 to - .18) was observed on the left and a small effect size of d= .02 (95%CI: - .05 to .09) on the right-side.



Box and Whisker plot showing the interquartile distribution

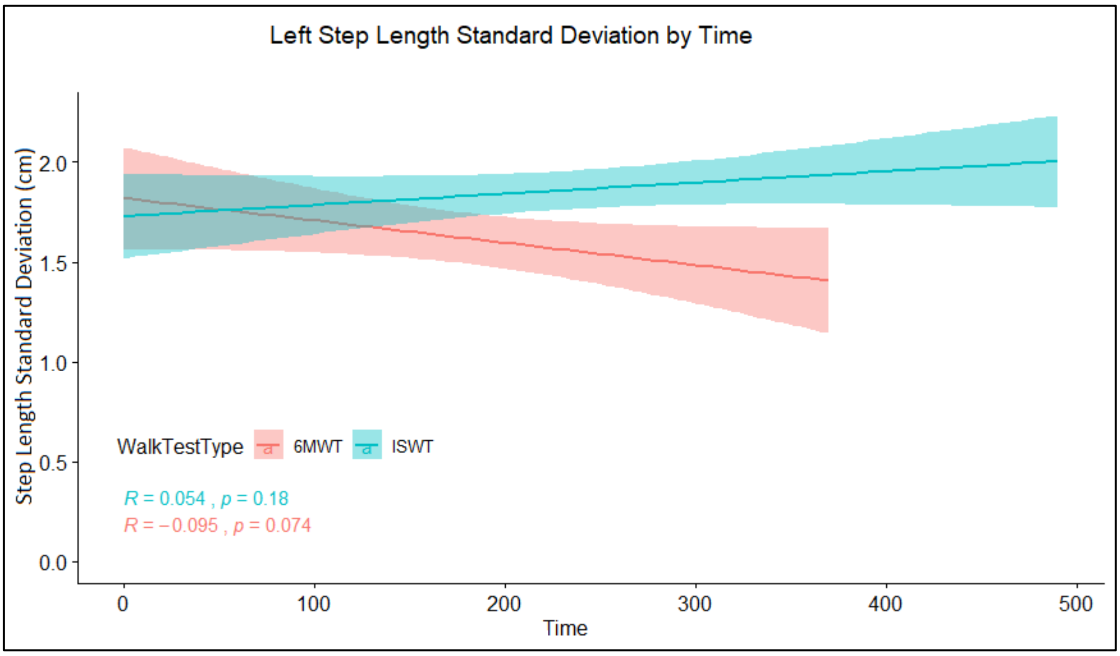
Figure 4.5a Left Step Length Standard Deviation (cm) at Start-Test and End-Test



Box and Whisker plot showing the interquartile distribution

Figure 4.5b Right Step Length Standard Deviation (cm) at Start-Test and End-Test

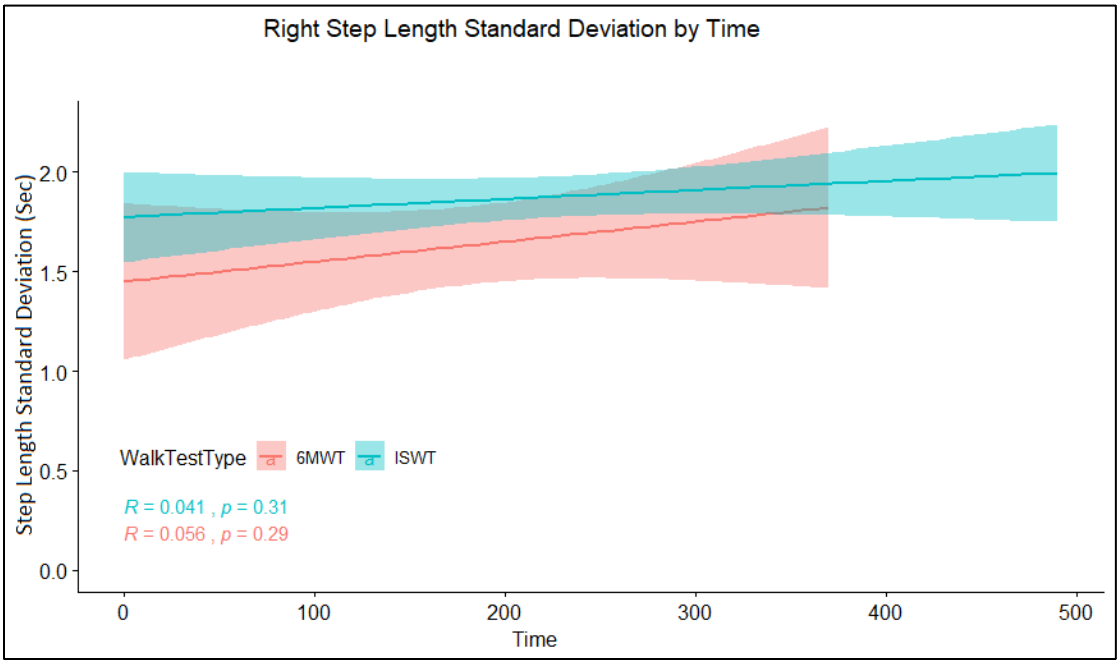
There was no association between left step length standard deviation and time, for either the 6MWT (r= .095, p= .074) or the ISWT (r= .054, p= .18) (Figure 4.5c).



Linear regression displaying mean and 95% CI

Figure 4.5c Left Step Length Standard Deviation Over Time

There was no association between right step length standard deviation and time, for either the 6MWT (r= .056, p= .29) or the ISWT (r= .041, p= .31) (Figure 4.5d).



Linear regression displaying mean and 95% CI

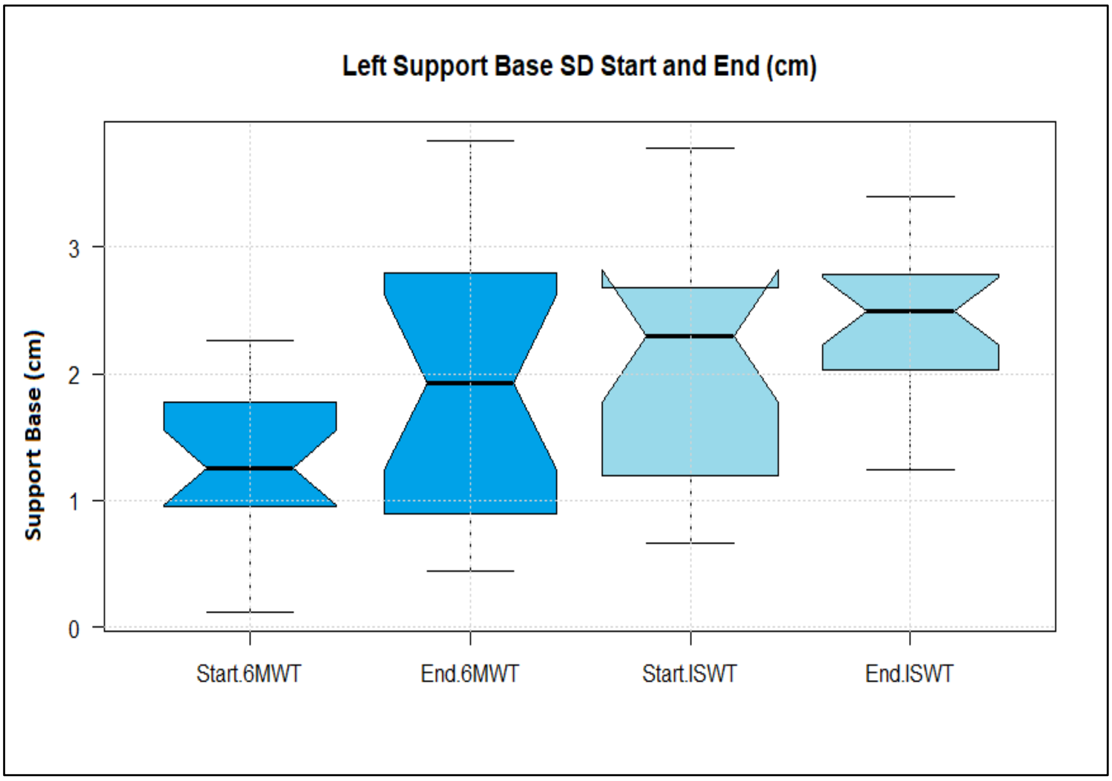
Figure 4.5d Right Step Length Standard Deviation Over Time

Support base standard deviation

The support base is measured as the horizontal width between footfalls at the phase in the gait cycle where both feet are in contact with the ground, measured in centimetres.

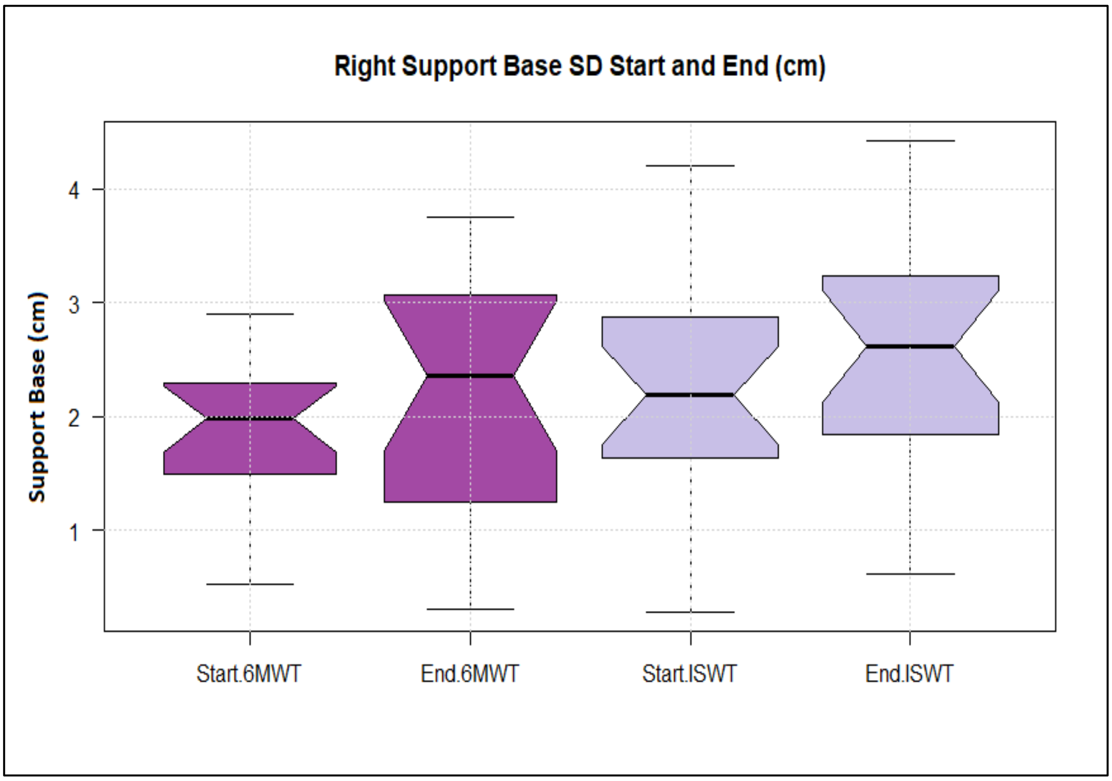
Support base standard deviation in the 6MWT had a start-test mean of 1.46 (± 0.88) cm on the left side and of 2.02 (±1.04) cm on the right side. End-test support base standard deviation for the 6MWT was 1.94 (± 1.10) cm on the left side and 2.13 (±1.09) cm on the right side (Figure 4.6a and Figure 4.6b, respectively). Cohen's d analysis showed a statistically small effect size from the start to the end-test mean of d= .16 (95%CI: .09 to .24) on the left side and d= .13 (95%CI: .06 to .21) on the right-side. Start to end test analysis (double-sided t-test) gave no significant change in support base standard deviation in the 6MWT on the left side p = 0.671 (95%CI: -0.438 to 0.283) or right-side p= .526 (95%CI: -0.516 to 0.265).

Support base standard deviation in the ISWT had a start test mean of 2.13 (±0.94) cm on the left side and 2.26 (±1.10) cm on the right side. End-test support base standard deviation mean for the ISWT was 2.36 (± 0.68) cm on the left side and 2.62 (± 1.01) cm on the right side. There was no significant change in ISWT start to end-test support base standard deviation distance p= .367 (95%CI: -0.486 to 0.181) for the left side and p= .847 (95%CI: -0.427 to 0.351) on the right side. A statistically small effect size of d= .18 (95%CI: .11 to .25) was observed on the left and d= .04 (95%CI: - .02 to .11) on the right-side.



Box and Whisker plot showing the interquartile distribution

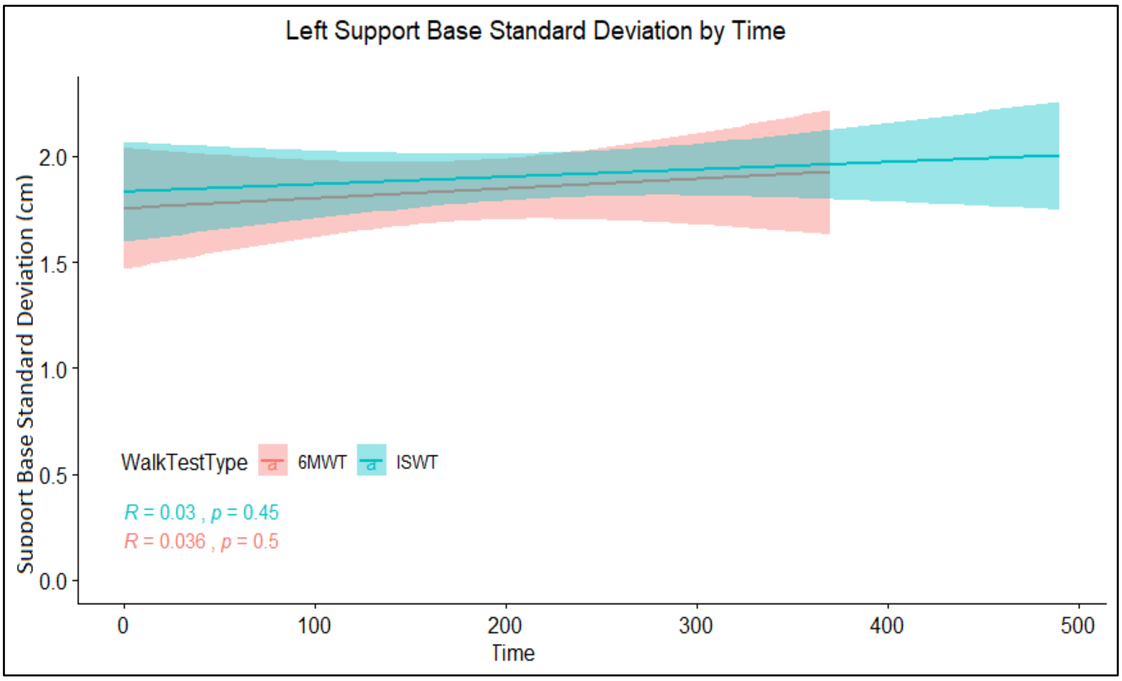
Figure 4.6a Left Support Base Standard Deviation (cm) at Start and End-Test



Box and Whisker plot showing the interquartile distribution

Figure 4.6b Right Support Base Standard Deviation (cm)at Start and End-Test

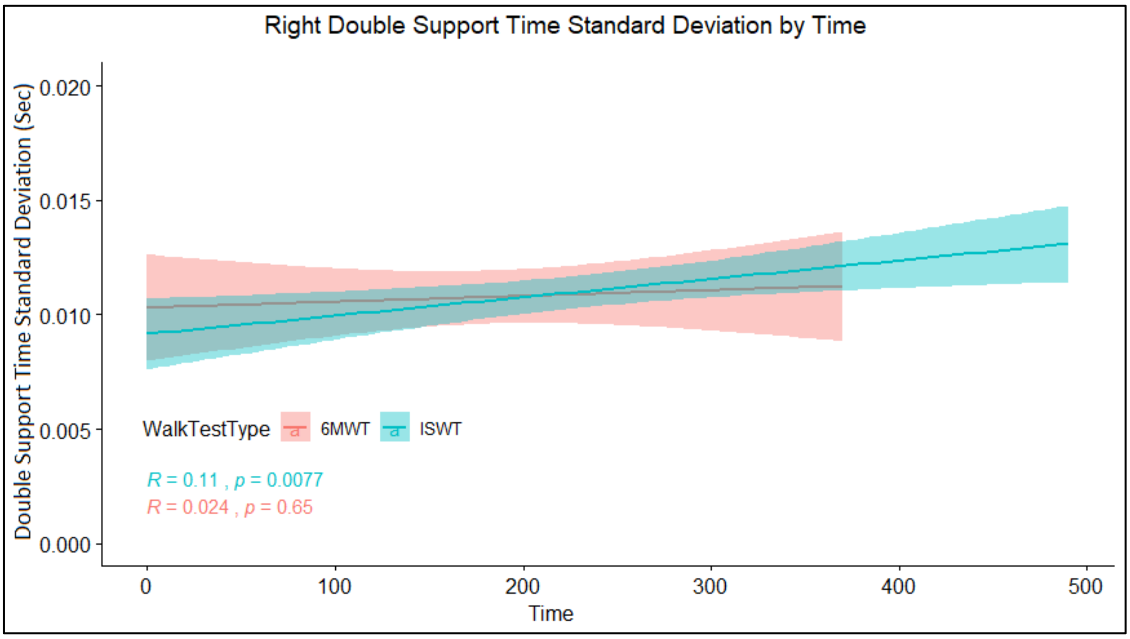
There was no association between left side support base standard deviation and time, for either the 6MWT (r= .036, p= .5) or the ISWT (r= .03, p= .45) (Figure 4.6c).



Linear regression displaying mean and 95% CI

Figure 4. 6c Left Support Base Standard Deviation Over Time

There was a small but statistically significant association between right-side support base standard deviation and time, for the ISWT (r= .11, p= .0077) but not the 6MWT (r= .024, p= .65) (Figure 4.6d).

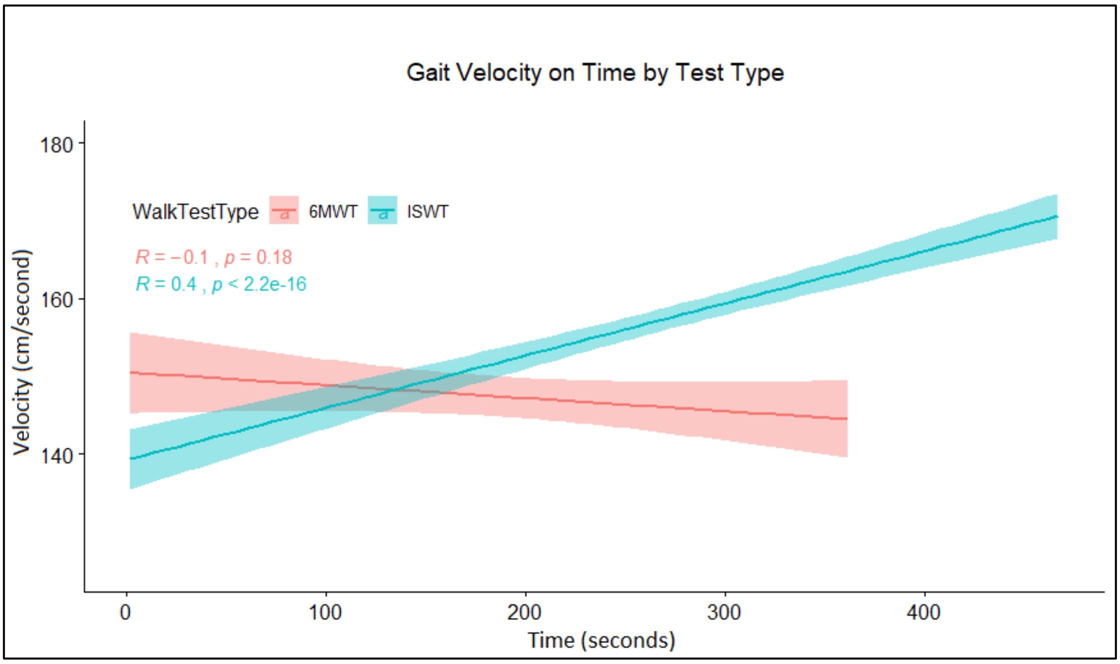


Linear regression displaying mean and 95% CI

Figure 4.6d Right Support Base Standard Deviation Over Time

Walking velocity by time

In the 6MWT mean walking velocity was 144.9 cm/s (±18.1) with a range of 93.4 to 181.6 cm/s. Walking velocity was mostly constant, with a gradual reduction over the duration of the test (Figure 4.7). A Pearson's product-moment correlation coefficient of velocity over time was r= -.1, but this small negative association was not statistically significant (p= .18). For the ISWT, mean walking velocity was 156.4 cm/s (±18.8) with a range of 92.8 to 213.3 cm/s. In the ISWT, walking velocity increases with time, A Pearson's product/moment correlation coefficient of velocity over time was r= .4, and this positive association was statistically significant (p= ≤.001) (Figure 4.7).



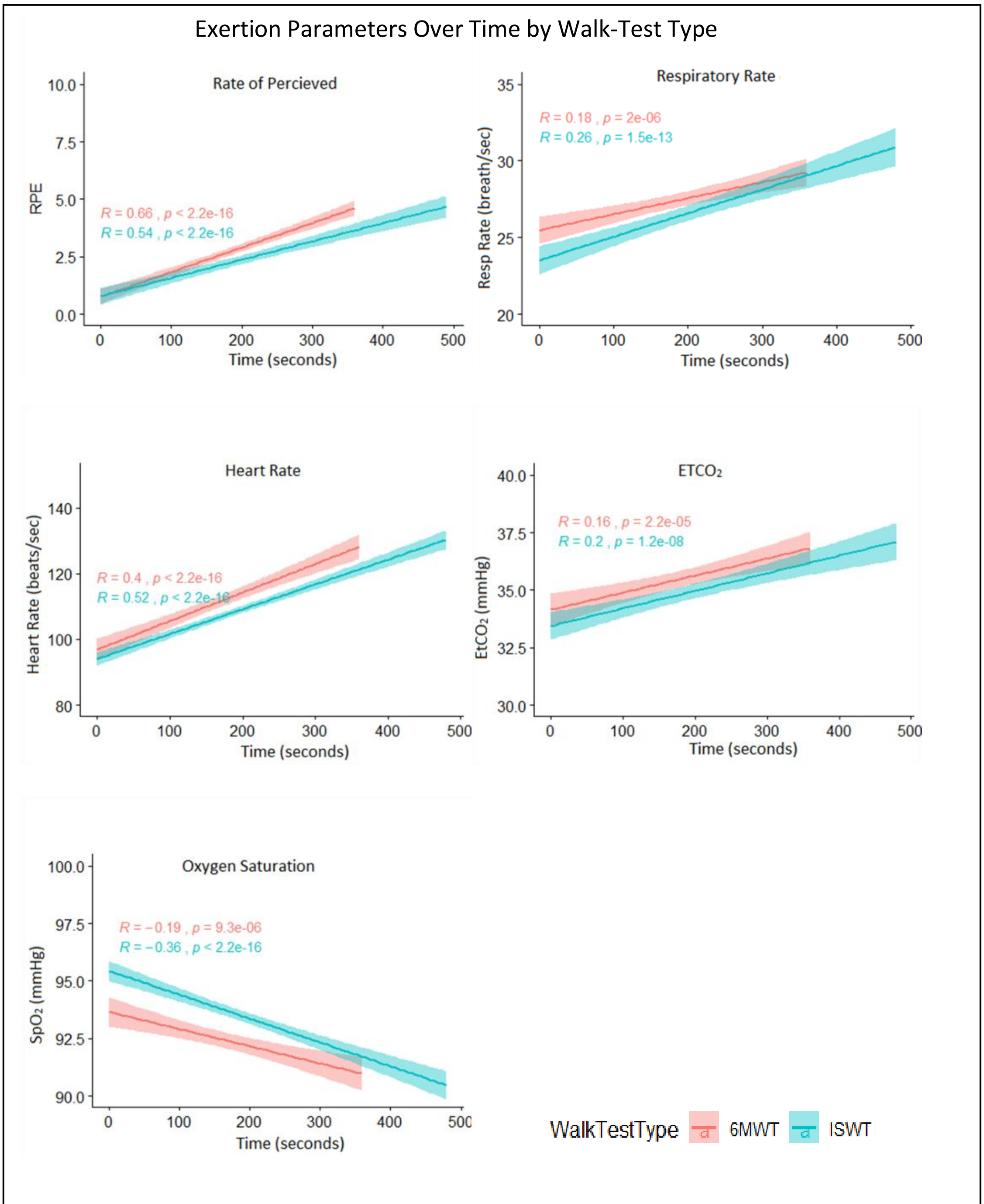
Linear regression displaying mean and 95% CI

Figure 4.7 Gait Velocity Over Time by Test Type

Exertion by time

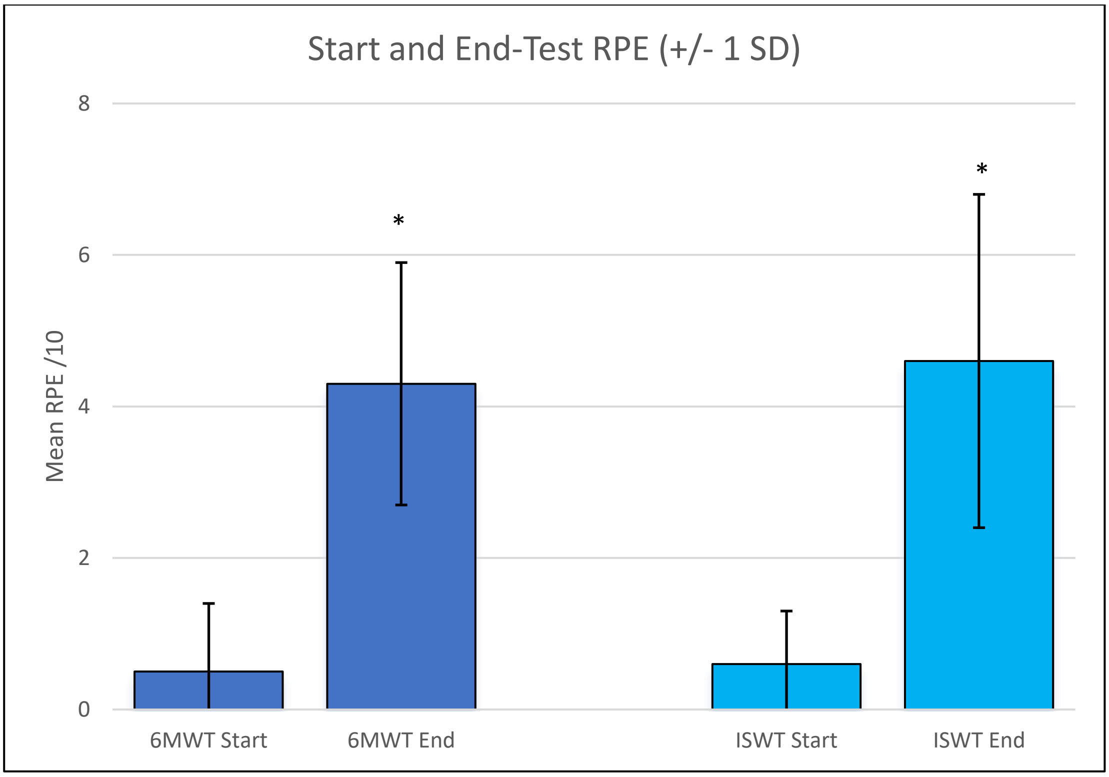
In the 6MWT, all measures of exertion increased over time (Figure 4.8). All measures except End Tidal Carbon Dioxide ($ETCO_2$) changed significantly from start to end-test (Figures 4.8a-e). Rate of Perceived Exertion (RPE) had a significant increase from mean 0.5 (±0.9) start-test to 4.3 (±1.6) post-test, p= .002 (95%CI: -2.21 to -0.52) (Figure 4.8a). Oxygen Saturation (SpO_2) decreased (indicating increased exertion) significantly from a mean of 95.5% (±2.2) to 92.2% (±4.6), p= .010 (95%CI: 0.49 to 3.46) (Figure 4.8b). This level of reduced SpO_2 may not be clinically significant in this population. $ETCO_2$ increased from 33.6 mmHg (±4) to 35.9 mmHg (±4.2) but failed to reach statistical significance p= .139 (95%CI: -2.89 to 0.41) (Figure 4.8c). Respiratory Rate (RR) significantly increased from a mean of 23.6 resp/min (±5.3) to 28.9 resp/min (±6.6), p= .006 (95%CI: -6.42 to -1.08) (Figure 4.8d). Heart Rate (HR) significantly increased from a mean of 92 BPM (±15.3) to 124 BPM (±17.5), p=0.004 (95%CI: -21.1 to -4.14) (Figure 4.8e).

In the ISWT, all measures of exertion increased over time (Figure 4.8), however from start- to end-test only two of the five measures (RPE and HR) reached statistical significance (Figure 4.8a-e). RPE increased significantly from mean 0.6 (±0.7) pre- to 4.6 (±2.2) post-test, p= .007 (95%CI: =-2.1 to -0.34) (Figure 4.8a). SpO_2 reduced (indicating increased exertion) from a mean of 95.9 % (±2.2) % to 90.7 (±4.3), p= .207 (95%CI: -0.56 to 2.54) (Figure 4.8b). $ETCO_2$ increased from 32.9 mmHg (±3.2) to 36.5 mmHg (±6) but failed to reach statistical significance p= .400 (95%CI: -2.5 to 1.00) (Figure 4.8c). The RR increased from a mean of 21.8 resp/min (±5.2) to 32.7 resp/min (±9.1). The increase may have clinical significance but failed to reach statistical significance p= .261 (95%CI: -4.76 to 1.31) (Figure 4.8d). HR significantly increased from a mean of 90 BPM (±15.3) to 123.4 BPM (±15.8), p= .034 (95%CI: -17.56 to -0.69) (Figure 4.8e).



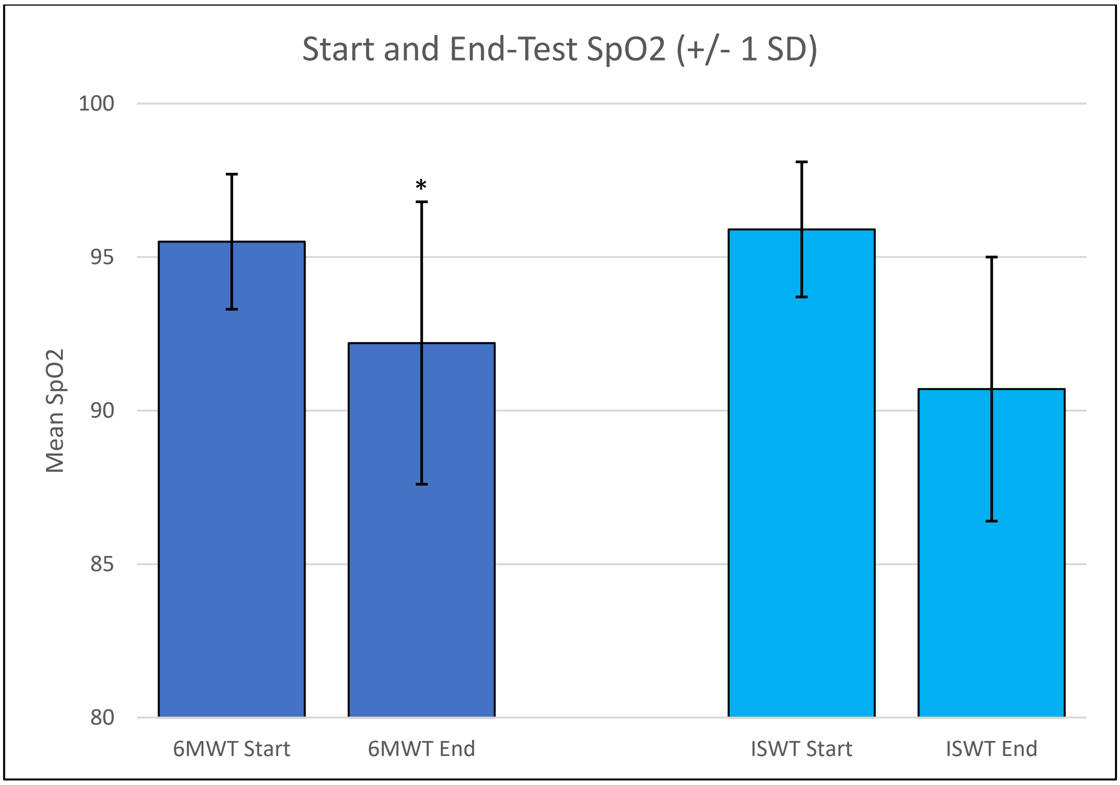
Linear regression displaying mean and 95%CI

Figure 4.8 Exertion Parameters Over Time by Walk-Test Type



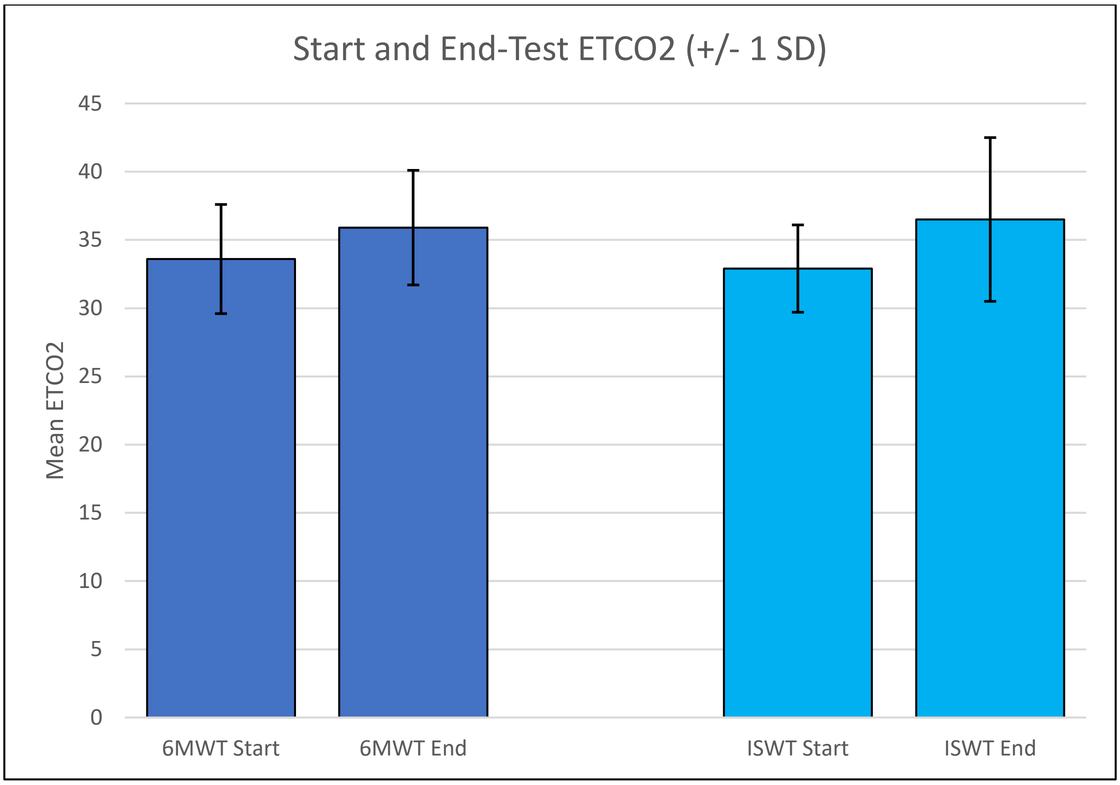
**Significantly different from baseline values (p≤.05)*
Method: Paired t-test (two sides)

Figure 4.8a Start and End Mean RPE by Walk-Test Type



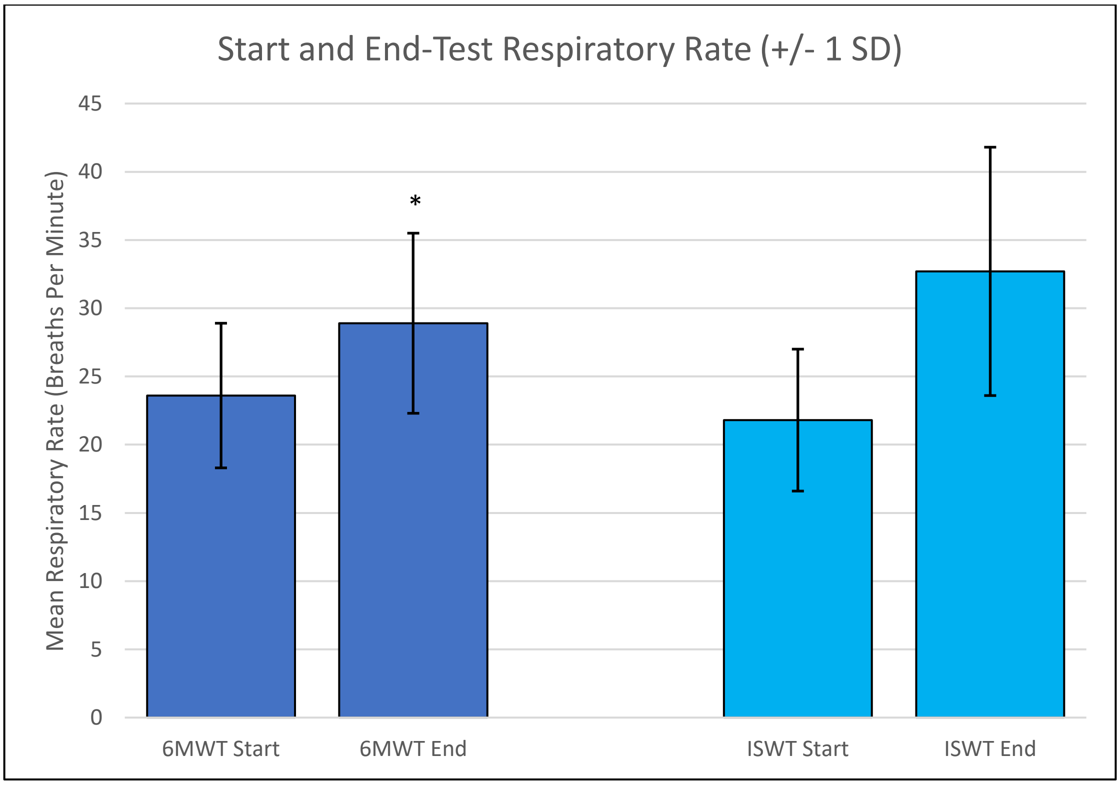
**Significantly different from baseline values (p≤.05)*
Method: Paired t-test (two sides)

Figure 4.8b Start and End Mean SpO_2 by Walk-Test Type



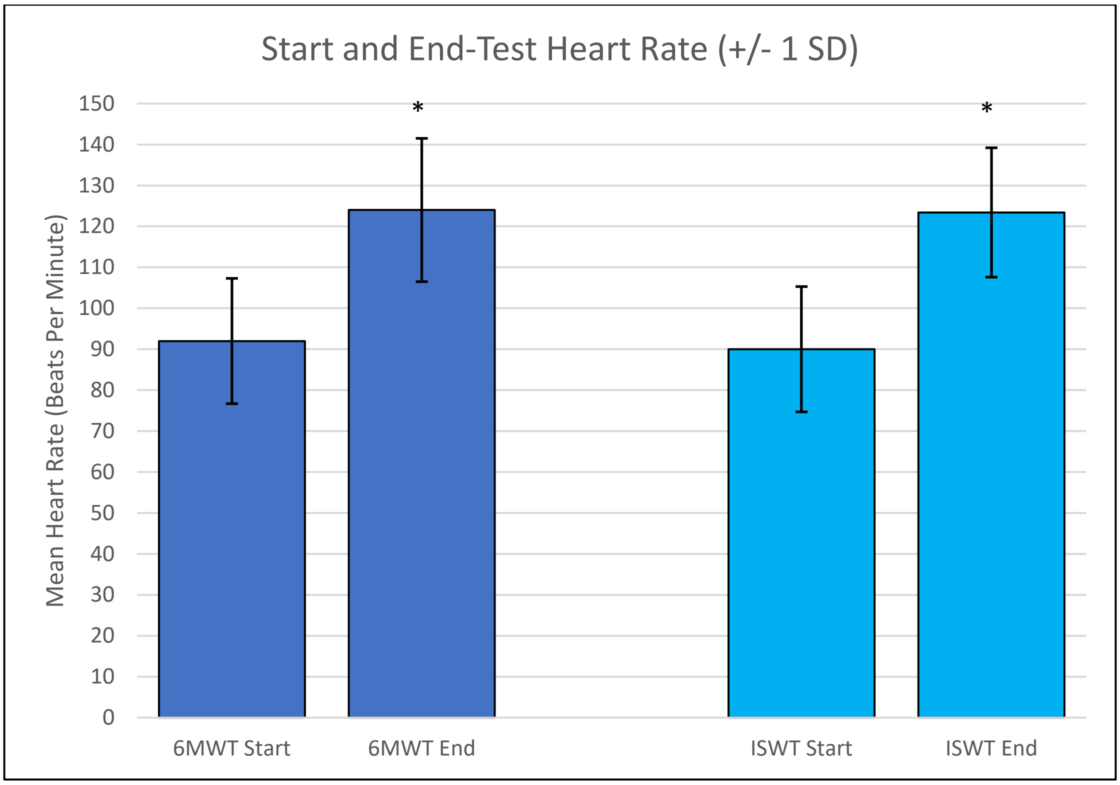
**Significantly different from baseline values (p≤.05)*
Method: Paired t-test (two sides)

Figure 4.8c Start and End Mean $ETCO_2$ by Walk-Test Type



**Significantly different from baseline values (p≤.05)*
Method: Paired t-test (two sides)

Figure 4.8d Start and End Mean Respiratory Rate by Walk-Test Type

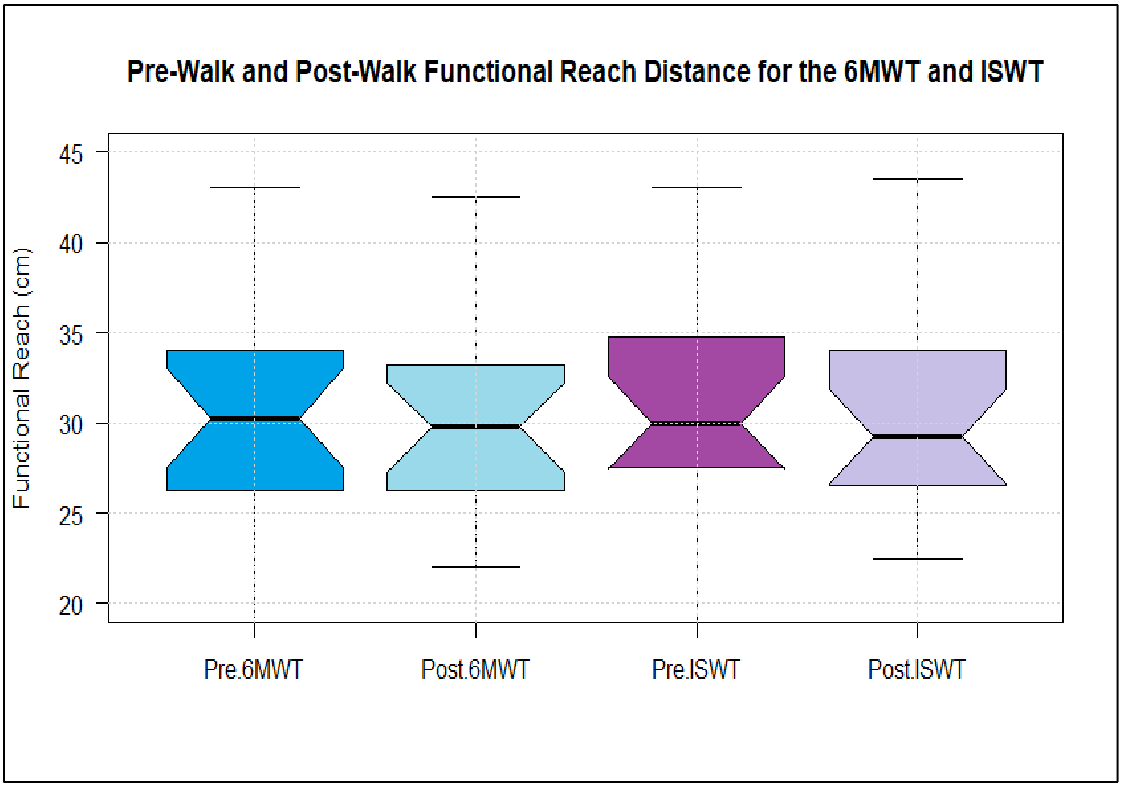


**Significantly different from baseline values (p≤.05)*
Method: Paired t-test (two sides)

Figure 4.8e Start and End Mean Heart Rate by Walk-Test Type

Dynamic balance pre and post-test

In the 6MWT pre-test Functional Reach (FR) mean distance was 30.08 cm (±6.15) and a post-test FR mean was 29.95 cm (± 5.08). A paired t-test (two sided) on pre- to post-test FR demonstrated no significant change in reach distance p= .860 (95%CI: -1.34 to 1.59) (Figure 4.9). Similar results were evident for the ISWT. Pre-test FR mean was 30.88 cm (±5.95) and post-test FR mean was 30.23 cm (±5.51). Pre-post FR analysis for the ISWT demonstrated no significant change in reach distance p= .463 (95%CI: -1.17 to 2.47).



Box and whisker plot showing mean and inter-quartile distribution

Figure 4.9 Pre and Post-Test Functional Reach in 6MWT and ISWT

Gait variability by exertion

Stance time standard deviation

Stance time standard deviation in the 6MWT had a small negative association, approaching significance with $ETCO_2$ (r= -.103, p= .053, 95%CI: -0.206 to 0.002) on the right site and a significant association with HR on the left side (r= -.143, p= .016, 95%CI: -0.257 to -0.027) (Table 4.4). No other significant associations with measures of exertion were observed for stance time standard deviation in the 6MWT. Stance time standard deviation in the ISWT had no significant association with measures of exertion except for RPE, which had a positive association of r= .133, p= .049 (95%CI: 0.001 to 0.262).

Table 4.4 Stance Time Standard Deviation versus Exertion Correlation Coefficient

		Left Side				Right Side			
Walk Test	Exertion	r. value	p. value	95%CI		r. value	p. value	95%CI	
6MWT	RPE	.055	.525	-0.115	0.223	-.031	.724	-0.199	0.140
	$ETCO_2$	-.103	.053	-0.206	0.002	.019	.719	-0.086	0.124
	SpO_2	.084	.162	-0.034	0.199	-.024	.690	-0.141	0.094
	RR	-.001	.987	-0.106	0.104	-.014	.796	-0.119	0.091
	HR	.020	.737	-0.097	0.137	-.143	.016*	-0.257	-0.027
ISWT	RPE	.072	.289	-0.061	0.203	.133	.049*	0.001	0.262
	$ETCO_2$	.052	.205	-0.028	0.131	.074	.071	-0.006	0.153
	SpO_2	.022	.598	-0.060	0.104	-.056	.182	-0.138	0.026
	RR	-.011	.781	-0.092	0.069	-.024	.565	-0.104	0.057
	HR	.060	.151	-0.022	0.142	.069	.099	-0.013	0.151

Method: Pearson's product-moment correlation. Alternative: two sided
** significant values (p≤.05)*

Stride time standard deviation

Stride time standard deviation had no significant linear relationship with measures of exertion for either the 6MWT or the ISWT on the left side (Table 4.5). On the right side, stride time standard deviation had a significant negative association with HR r= -.164, p= .006 (95%CI, -0.276 to -0.047) in the 6MWT but not the ISWT, and a significant positive association with $ETCO_2$ in the ISWT only r= .104, p= .011 (95%CI: 0.024 to 0.182).

Table 4.5 Stride Time Standard Deviation versus Exertion Correlation Coefficient

		Left Side				Right Side			
Walk Test	Exertion	r. value	p. value	95%CI		r. value	p. value	95%CI	
6MWT	RPE	.021	.814	-0.150	0.189	.030	.733	-0.141	0.198
	$ETCO_2$	-.011	.838	-0.115	0.094	-.028	.599	-0.132	0.077
	SpO_2	.001	.993	-0.117	0.118	.002	.979	-0.116	0.119
	RR	-.024	.652	-0.129	0.081	.003	.954	-0.102	0.108
	HR	.016	.785	-0.101	0.134	-.164	.006*	-0.276	-0.047
ISWT	RPE	.111	.102	-0.022	0.241	-.011	.877	-0.143	0.123
	$ETCO_2$	-.009	.820	-0.089	0.071	.104	.011*	0.024	0.182
	SpO_2	.025	.551	-0.057	0.107	.017	.685	-0.065	0.099
	RR	.039	.347	-0.042	0.119	-.050	.220	-0.130	0.030
	HR	.067	.109	-0.015	0.149	.051	.221	-0.031	0.133

Method: Pearson's product-moment correlation. Alternative: two sided
** significant values (p≤.05)*

Swing time standard deviation

Swing time standard deviation had no significant association with measures of exertion for the left or right side for either the 6MWT or ISWT (Table 4.6). In summary, there was no clear observable linear association between left or right-side stride, stance, or swing time fluctuations and measures of exertion in either the 6MWT or ISWT, despite a clear statistically significant pattern of increasing exertion for both walk tests.

Table 4.6 Swing Time Standard Deviation versus Exertion Correlation Coefficient

		Left Side				Right Side			
Walk Test	Exertion	r. value	p. value	95%CI		r. value	p. value	95%CI	
6MWT	RPE	.088	.310	-0.082	0.254	.063	.470	-0.108	0.230
	$ETCO_2$	.026	.621	-0.078	0.131	-.058	.279	-0.162	0.047
	SpO_2	-.077	.200	-0.193	0.041	.058	.338	-0.060	0.174
	RR	-.052	.336	-0.156	0.054	.048	.374	-0.057	0.152
	HR	-.021	.727	-0.138	0.097	-.017	.771	-0.135	0.100
ISWT	RPE	.114	.093	-0.019	0.243	-.009	.892	-0.142	0.124
	$ETCO_2$	-.012	.767	-0.092	0.068	.041	.318	-0.039	0.121
	SpO_2	.006	.886	-0.076	0.088	.013	.751	-0.069	0.096
	RR	.012	.764	-0.068	0.093	-.027	.513	-0.107	0.054
	HR	-.060	.156	-0.141	0.023	-.021	.625	-0.103	0.062

Method: Pearson's product-moment correlation. Alternative: two-sided
** significant values (p≤.05)*

CHAPTER 5

Discussion

The primary aim of this research was to determine if people with COPD are at an increased risk of falling during activities that require increased exertional effort. Risk of falling in COPD as measured by gait variability did not change with exertion in either the 6MWT or ISWT. Also, balance control did not change after completing either of these exertional walking tests. Although participants demonstrated high levels of exertion, these results indicate participation in these exertional walking assessments does not increase the risk of accidental falls beyond baseline exertion levels. As walking regularity does not degrade from baseline levels, this original research supports the continued use of either walking test in a community-dwelling COPD cohort.

Primary aims

Gait variability

Stance time, double support time, and step length did not deteriorate from the start of the exertional walking tests to the end of the tests in this study. These gait measures are validated falls risk predictors (Marques et al. 2018) and were chosen to comprehensively map the footfall pattern throughout the gait cycle. As a single gait variable, stance time standard deviation has greater sensitivity and specificity to falls than gait speed, stride length, single limb support time, and double limb support time (Marques et al. 2018). Marques et al. (2017) identified a cut-off value of 0.102 seconds for stance time standard deviation (from heel strike to toe-off) to discriminate between fallers and non-falling older adults (sensitivity/specificity = 100/100%, $p = \leq .001$). In this study, there was no increase in baseline levels of gait variability despite participants reaching maximum levels of exertion. The hypothesis that as people with COPD increase their level of exertion during walking tasks, their gait regularity decreases is not supported. This result indicates that the risk of sustaining an accidental fall does not further increase during exertional walking tests in the COPD population.

This research finding supports the ongoing use of exertional walking tests to measure the positive health benefits of pulmonary rehabilitation participation. Until now, there was little evidence available to determine if walking with increased exertion during assessment increases gait variability and increases risk of falling. Pulmonary rehabilitation by design increases exertion levels. Both the 6MWT and ISWT are regularly used in pulmonary rehabilitation and are accepted measures of exercise capacity (Brown & Wise 2007; Ho & Maa 2016). Results from the present study demonstrate that participation in both tests (in a controlled environment) does not increase gait variability from baseline, nor does it increase the risk of accidental falls. A possible mechanism behind this is that people are self-regulating their activity exertion levels to enable them to operate within a safe exercise tolerance boundary with respect to balance control.

Dynamic balance

Functional reach (FR) distance showed no significant change from pre-test when levels of exertion were low to post-test, when exertion levels were high, in either of the exertional walk tests. This result indicates balance activities conducted in pulmonary rehabilitation in addition to exertional walking type activities are not likely to result in a reduction of balance control from baseline exertion levels. The reach test was chosen as a self-generated perturbation measure of dynamic balance because it can be administered quickly while exertion levels are transiently elevated and for its utility as a predictor of recurrent falls (Duncan et al. 1992). The hypothesis that dynamic balance deteriorates in response to exertional walking was not supported, further indicating that falls risk does not increase in this population as a result of participating in commonly used exertional walk tests.

The current study indicates that balance control does not diminish as a result of increased exertion. This is surprising, because people with COPD have poor dynamic balance compared to healthy older adults (Beauchamp et al. 2012; De Castro et al. 2016; Voica et al. 2016) and high accidental falls rates (Hakamy et al. 2018; Sousa et al. 2017). Until now, there was a sparsity of evidence available to show that balance activities are safe during periods of elevated heart rate, respiratory rate, and rate of perceived exertion. This has implications for including balance activities in pulmonary rehabilitation programs safely, as programs with a balance training component improve dynamic balance and reduce falls risk (Hill 2014; Marques et al. 2015; Mkacher et al. 2015).

Secondary aims

Relationship between gait regularity and exertion level

There was no significant linear correlation between gait variation and changing levels of exertion throughout either the 6MWT or ISWT. Stance, stride and swing time were used as measures of gait regularity because they are sensitive to differentiate between fallers and non-fallers (Marques et al. 2018). The 6MWT and ISWT were chosen as exertional walking tests, as they are the most commonly employed to provoke exertion (Ayiesah & Chang 2010; Brown & Wise 2007; Ho & Maa 2016). The hypothesis that there is an identifiable relationship between the level of exertion and gait regularity during exertional walking was not supported in the present study.

Participants in the current study demonstrated the ability to self-regulate their exertion levels during effortful walking to prevent reductions in gait regularity. This finding supports previous studies that show the 6MWT and ISWT to be associated with few fall events despite increasing exertional parameters such as exertion-induced oxygen desaturation (Afzal et al. 2018; Jenkins & Čečins 2011). Jenkins and Čečins (2011) identified that exercise induced oxygen desaturation (≥4% fall in SpO_2 to < 90%) to be prevalent (50%) in COPD during 6MWTs but with no reported accidental falls. A similar study analysing records from a large pulmonary rehabilitation population found that desaturation even below SpO_2 of 80%, was not associated with accidental falls (Afzal et al. 2018). This study adds to the evidence that the high rate of falls in the COPD population may result from other factors than the reduction in circulating oxygen levels. Some authors postulate that central nervous lesions from vascular abnormalities and not impaired respiratory function, may be responsible for increased fall rates in people with COPD (Morlino et al. 2017).

Gait variability and velocity

Double support time, step length time, and support base standard deviation did not significantly change from pre- to post-test for either the 6MWT or the ISWT or in proportion to increasing velocity in the ISWT. The ISWT had a linear increase in velocity with a significant change in pre- to post-test velocity ($p = \leq .001$) whereas the 6MWT had a more uniform velocity with no statistically significant change throughout the tests. Gait variability has been described as the most sensitive gait parameter to differentiate between fallers and non-falling older adults (Marques et al. 2018). In the current study, no obvious pattern of change in gait variability occurred despite participants walking at their sustained maximum pace in the 6MWT or when walking at increasing velocities to the point of voluntary failure in the ISWT. This clinically important result demonstrates that the risk of falling does not rise from baseline levels when self-governed incremental increases in gait velocity occur.

Exertion – in the six-minute walk test and incremental shuttle walk test

In the 6MWT, perceived rate of exertion, heart rate, and respiratory rate all increased significantly from start-test to end-test and oxygen saturation significantly dropped, but there was no significant change in end-tidal carbon dioxide levels. The exertion profile was different for the ISWT as only perceived rate of exertion (RPE) and heart rate (HR) changed significantly from start-test to end-test readings. For the exertion profile, RPE was selected as a self-rated measure of effort; the respiratory rate (RR) for ventilatory demand; heart rate (HR) as a measure of exercise intensity; oxygen saturation (SpO_2) for aerobic capacity; and End-Tidal Carbon dioxide ($ETCO_2$) for evidence of ventilatory compromise. The 6MWT and the ISWT were chosen as exertional walking tests to analyse and contrast gait variability at sustained maximal exertion as well as at incrementally increasing levels of exertion to the point of voluntary failure. Researchers in the present study selected the ISWT to analyse gait variability at maximum exertion and avoid the possibility that gait variables did not change due to an insufficient elevation in exertion. It is clinically significant that gait regularity remained constant from start-test (low exertion) to end-test (self-governed maximal exertion). This is because exertional walking tests commonly underpin assessment of functional capacity (Andrianopoulos et al. 2015; Brown & Wise 2007; Ho & Maa 2016), guide intensity levels during pulmonary rehabilitation (Gloeckl, Marinov & Pitta 2013; Zainuldin, Mackey & Alison 2015), and are used as a predictor of disease prognosis (Celli et al. 2016; Dajczman et al. 2015).

Exertional walk tests when used in the clinical management of COPD commonly measure SpO_2, HR, and RPE. Measurement of $ETCO_2$ is less common in the sub-acute setting as it requires capnography equipment. In this study, controlled steady-state walking during the 6MWT appeared to have less impact on RR and SpO_2 than in the progressive ISWT. The ISWT produced a larger range in RR and SpO_2 than the 6MWT, but neither test resulted in exercise-induced hypercapnia. $ETCO_2$ levels increased in response to exertional walking but without statistical significance in either walk test. This result may indicate that the onset of hypercapnia has a larger impact on the perception of exertion and that participants reduced their intensity to prevent the onset of hypercapnia. Despite the different exertion profiles between the walk tests, neither test observed a significant change in gait variability with self-governed exertion. This result can be used to guide current management of people with moderate COPD, as it indicates that baseline level of falls risk does not change during exertional walking and that measurement of SpO_2, HR, and RPE adequately give direction on safe intensity levels.

Comparisons and contrasts to current literature

Gait variability

This was the first study to give a direct comparison of gait variations at different levels of exertion in a community-dwelling COPD cohort of mostly moderate severity. The novel component of the present study was the direct comparison of gait variability in COPD measured at the beginning of a walk test (low-level exertion) to gait variability at the end of a walk test (high level of exertion). The present study found no statistical difference in stride to stride fluctuations for stance time, double support time, and step length from the start of the walk tests to the end, meaning gait variability was unchanged from low-level exertion to the peak of self-governed high exertion. Stance, double support time, and step length variability have been validated as independent predictors of fallers in community-dwelling adults (Marques et al. 2018; Mignardot et al. 2014; Mortaza, Abu Osman & Mehdikhani 2014) but not measured in COPD at varying levels of exertion. Currently, there is an absence in the literature of normative values for gait variability in COPD (Zago et al. 2018). Most contemporary studies on gait variability in COPD give a comparison between COPD gait to healthy controls (Table 5.1) rather than in varying states of exertion.

Table 5.1 Measures of gait variability found to be impaired in COPD

Spatiotemporal gait variable	Finding Summary	Study/s
Step time variability	• COPD had longer step time with shorter length (slower over ground velocity) than control participants • COPD had increased time between steps and more variable than control participants	(Rutkowski et al. 2014; Yentes et al. 2017)
Step width variability	• COPD had reduced width and decreased variability compared to controls	(Yentes et al. 2017; Yentes et al. 2015)
Step length variability	• COPD had increased variability in step length compared to controls • Shorter step length than controls	(Morlino et al. 2017; Rutkowski et al. 2014)
Stride time variability	• COPD had increased variability in stride time while dual tasking • COPD fallers had more variability than non-fallers • Stride time variability increased with COPD severity	(Heraud et al. 2018; Lahousse et al. 2015; Liu et al. 2017)
Stride length variability	• COPD had increased stride length variability compared to healthy participants after correction for speed	(Liu et al. 2017)
Time in double support	• COPD compared to healthy controls had increased double support time and variability	(Nantsupawat et al. 2015) (Liu et al. 2017)
Self-selected walking velocity	• Gait speed reduces with COPD severity	(Ilgin et al. 2011; Karpman & Benzo 2014)

Dynamic balance – Functional reach Test

FR distances did not change in response to participation in either of the exertional walk tests and fell within expected distances, considering their demographics and the presence of COPD. The mean of all FR distances measured in the present study (before and after the longest walk tests) was 30.28 cm (±5.6) and the mean age was 70.8 years (±8.2). A systematic review and meta-analysis on normal values for the FR test gives 26.6 cm (95%CI: 25.14 to 28.06) as a reach test for community-dwelling older adults but found reach distance to be significantly affected by age (but not sex) (Rosa, Perracini & Ricci 2019). Isles et al. (2004) gives an age-adjusted normative FR score of 34.13 cm (±0.54) for persons 70-79 years. Given that a large COPD cohort study found the presence of COPD to reduce FR distance across all ages by 3.0 cm (95%CI: 4.2 to 1.8) (Eisner et al. 2008), the mean FR distance in the present study was within an expected range typical for a person 70 years old and with COPD.

Using the FR test as a description of dynamic balance in the COPD cohort was a novel but feasible application of the test. The FR test is a measure of self-generated perturbation (Duncan et al. 1992) but does not appear commonly in the COPD literature. Despite this, a positive correlation between dynamic balance impairment and greater falls incidence has been established in COPD (Beauchamp, Brooks & Goldstein 2010; Beauchamp et al. 2009; Porto et al. 2017).

The primary reason for selecting the FR test was to capture any transient change in dynamic balance control near peak exertion. There is no consensus on the most sensitive balance assessment tool for determining risk of falling in COPD (Beauchamp 2019), however the BESTest, Mini-BESTest, Berg Balance Scale, and Brief-BESTest are validated identifiers of fall status in COPD (Jácome et al. 2016) as is the Timed Up and Go Test and Single Leg Stance Test (Beauchamp 2019; Beauchamp et al. 2009; Porto et al. 2017). Neither of these tests could be utilised in the present study, as they are not able to capture changes in control of self-generated perturbation during a brief period while exertion levels are high.

Gait variability, exertion level, and velocity

No clear pattern of association was identified in the present study between gait regularity and level of exertion at a consistent speed (6MWT) or at increasing speed (ISWT). This finding is consistent with a study measuring gait parameters in healthy older adults at comfortable walking speeds during a maximal exhaustive walking test, and again walking for 2 kilometres (Donath et al. 2013). In all three test conditions, stride frequency, stride width, double stride time and length, along with double stance length had a significant change in regard to test condition and post hoc analysis (Donath et al. 2013). These results contrast findings from a small study of healthy people who had spatiotemporal gait measures, HR, and RPE recorded during six-minutes of fast walking (Nagano et al. 2014). Results from this study show step length, double support time, and step width variability to increase with fatigue (Nagano et al. 2014). The exact mechanism behind discrepancies in research investigating gait regularity response to exertion is unclear. A study with a largely homogeneous population may be required to determine a clear response pattern.

A unique component of the current study is the utilisation of self-paced and externally paced intensity as well as spatiotemporal gait measurement at different walking velocities. The study design shows that self-paced walking from the 6MWT is comparable to the ISWT in its ability to evoke a change in exertional parameters and because the ISWT incrementally escalates in exertion and velocity until the point of voluntary failure several key comparisons can be made between the two walking tests.

Firstly, the comparative study design addresses the hypothesis that exertion levels are relational to gait variability. Prior to this study, gait variability is usually observed at self-selected pace and does not account for walking with increased effort or at a greater velocity (Lahousse et al. 2015; Yentes et al. 2011; Yentes et al. 2015). Exceptions to this trend either describe gait near steady-state walking pace such as in a 6MWT (Beauchamp et al. 2009; Liu et al. 2017; Morlino et al. 2017) or at fixed thresholds above and below self-selected walking pace (Yentes et al. 2017). The present study found no degradation in gait variability despite a clear and uniform increase in effort and gait velocity.

Secondly, the study findings are more clinically meaningful with the incorporation of both walking tests as increased or decreased velocity could been observed as a compensatory response for degrading dynamic balance control. Findings form this study show that gait regularity did not change in response to walking velocity or effort as there was no significant change in magnitude of stance, stride, or swing time standard deviation means from start to end-test measures (in either walking tests). This result is consistent with a study that found 30 minutes of walking at self-selected did not change gait variability (Da Rocha et al. 2018) and a study that found those with COPD regulated there self-selected walking speed to maintain a tolerable level of dyspnoea (Sanseverino et al. 2018).

Lastly, the study methodology used in this study gave a comparable measure in comfortable self-paced and pushed effortful walking. Studies that only use self-selected pace to evoke a change in spatiotemporal gait parameters are likely to observe changes caused by fatigue rather than a sharp and pushed rise in exertion. Findings from the present study indicate that walking velocity in those with COPD is modulated and limited to maintain a tolerable exertion level (or level of dyspnoea) rather than to sustain an adequate level of dynamic walking stability. This supposition is based on the finding that there was a spike in most effort parameters including the RPE for both walking tasks but an apparent consistency in gait variability for both walking tests. The clinical ramifications of this finding are that participation in activities such as pulmonary rehabilitation may be effective in increasing exertional thresholds and result in confidence to increase walking velocity.

The current study has a unique finding of no change in spatiotemporal gait variability despite a statistically significant change in exertion in both walk tests and velocity in the ISWT. A comparison study of 80 people with COPD and 38 healthy age-matched controls participated in a 6MWT with analysis from the Gait Real-time Analysis Interactive Lab (Liu et al. 2017). Those with COPD (mostly moderate to severe) had reduced stride and step length, as well as increased gait variability, compared to healthy older adults, even after correction for walking speed between groups (Liu et al. 2017). The study methodology differed from the present study in that it did not investigate within test differences of gait variability for the COPD group and gave no comparison measures of gait at differing walking velocities. In contrast, Yentes et al. (2017) conducted gait analysis at three walking speeds: self-selected and ± 20% of self-selected speed. Results revealed the COPD cohort to walk with longer step time with increased step time variability than the control group. Yentes et al. (2017) also found that step width was narrower at slow speed and wider at a faster speed in COPD, and this trend was reversed for the control group. Again, study methods varied from the present study in that it was conducted on a treadmill, the testing was at set velocities, the velocity range was limited, and the study focus was a comparison between disease and control groups rather than changes within disease group in response to exertion.

Exertion Levels

There was a marked change in exertion levels for the 6MWT, as HR, RR, and SpO2 all significantly changed statistically from start-test to end-test were as in the ISWT only RPE and HR changed statistically from start-test to end-test. This result differs from a study that compared the cardiovascular (HR) and respiratory (RPE) exertional responses of the 6MWT to the ISWT and found no statistically significant difference between the tests (Hodgev et al. 2003). A similar peak exercise response between the 6MWT and ISWT has been observed in some (Hill et al. 2012; Luxton et al. 2008; Turner et al. 2004), but not all historic studies (Onorati et al. 2003; Singh et al. 1992). One study argued the ISWT is more accurate than the 6MWT for evaluating maximal exercise tolerance in COPD (Onorati et al. 2003). Despite the differing exertion profiles of the exertional walk tests, there was no observable pattern of change in gait variability for either test, inferring no correlation between self-governed exertion and gait variability in COPD.

Strengths of methodology

Innovative and comprehensive measurement of exertion, gait, and balance

The investigation is important because exertional walking tests underpin the functional assessment of COPD and guide pulmonary rehabilitation intensity. This study directly compares measures of exertion with gait variability and balance, and exertion was measured comprehensively. Preceding studies typically describe COPD gait variability in comparison to healthy controls rather than in response to exertion (Liu et al. 2017; Morlino et al. 2017; Yentes et al. 2017). There are few studies describing normative values for gait in COPD (Zago et al. 2018) and none comparing gait variability directly to exertion levels despite exertional walk tests being common in clinical management. Several different measures of exertion were used to determine if one component of exertion had a larger influence on falls risk than another. The novel use of portable pulse oximetry and capnography enabled study participants to walk across a gait-mat at self-selected velocity unimpeded at a natural walking pattern at their own velocity (unlike treadmill walking). This study is the first to indicate that standing balance with self-perturbation does not deteriorate even directly after performing a high intensity walking task. A possible mechanism behind this is that people can self-regulate their activity exertion levels to enable them to operate within a safe exercise tolerance boundary.

Safe investigation of a falls risk factor

Researchers in the current study safely investigated known falls risk factors to levels of exertion (commonly experienced during exercise testing) in a population with a demonstrated propensity to accidental falls and vulnerability to injury. This research was conducted in an ethically sound and safe manner through close supervision of walking regularity, guarding dynamic balance control measurement, and constant monitoring of exertion levels to ensure they remained within safe parameters. It was important to reach exertion levels near-maximum capacity to adequately prove or disprove the hypothesis of a correlation between exertion and walking variability and dynamic balance control. The study method enabled comparison between maximum exertion to voluntary failure from increasing velocity (using the ISWT) and a sub-maximal test of aerobic capacity (using the 6MWT). Researchers also acted prudently by selecting exertional walk tests that had a demonstrated low level of adverse events (Afzal et al. 2018; Brown & Wise 2007; Jenkins & Čečins 2011). The 6MWT is the most commonly used measure of exercise capacity for COPD in Australia (Holland et al. 2014; Singh et al. 2014) and the ISWT was chosen in addition to the 6MWT because it is a test of maximum exercise capacity, is externally paced, and incrementally increases in intensity to a point at which people reach voluntary failure (Brown & Wise 2007).

The use of capnography in the capture of exertion profile

Utilising capnography to measure $ETCO_2$ and RR during walking gave reliable and accurate data collection, as using pulse oximetry in the COPD cohort can present clinical difficulties. Absent or false readings from pulse oximetry can occur in people with anaemia (Hakemi & Bender 2005), poor peripheral circulation, hypothermia, during rapid desaturation (Jensen, Onyskiw & Prasad 1998), and when oxygen saturation levels are low (Smith & Hofmeyr 2019). There is reported accuracy limitations in pulse oximetry in anaemic people with COPD (Copur et al. 2015) and in the current study it was observed that SpO_2 readings at times failed to register a reading. The use of capnography gave a reliable measure of $ETCO_2$, enabled continuous capture of RR, and comparison between two commonly used respiratory measures of exertion.

Limitations of methodology

Gait variability and dynamic balance

There are limitations in the study from assessing gait using a gait sensor mat, and balance using the FR test. Gait measurement only captures overground footfall patterns and consequently does not measure balance adaptations made by the hips, trunk, or upper limbs. Technologies such as accelerometer-based methods have been used since the late 1990s to map the movement of different body parts during locomotion (Moe-Nilssen 1998), and reference data has been established for healthy populations (Auvinet et al. 2002). Depth-sensing cameras have been used to detect body movement during the gait cycle. 3D motion analyses have also been utilised to measure spatiotemporal gait characteristics of people with COPD and identified people with COPD to have increased gait variability as compared to healthy age-matched individuals (Liu et al. 2017). This testing method does not replicate community-dwelling or home environments and limits interpretation.

Conditioning of study participants

Study participants were recruited from a well-established pulmonary rehabilitation program and were compliant with exercise therapy. Testing these participants may produce a possible selection bias and give a sample of gait variability that is more stable in response to exercise-induced exertion than from a broader population. The sample population in the present study was possibly not at risk of exercise-induced hypercapnia either, as only one participant had a GOLD ranking of 4 (very severe) and the rest on average had moderate severity. A limitation of the data is that the findings presented may not be true for people with more advanced disease, those who are less compliant with therapy, or those who are more susceptible to falls.

Study size and scope

The present study was a pilot study of 20 participants recruited from pulmonary rehabilitation with small and unequal numbers across each of the GOLD rankings. There were insufficient numbers in the study to stratify participants by different characteristics of COPD to compare gait variability in different disease severity, phenotype, or fallers versus non-fallers. The participants recruited were predominantly in moderate GOLD stratification and it is known that those with a mild GOLD stratification have better balance control, are less prone to falls than a population with a higher disease stratification (Horie et al. 2011) and have improved capability to perform functional tasks (Souza et al. 2018). It is possible that increased gait variation may be observed in a COPD cohort that have more advanced COPD, are more susceptible to fatigue, and more likely to fall. The present study also had insufficient numbers to stratify participants by phenotype. One study identified that people with bronchitic dominant COPD have more falls than emphysematous COPD (Voica et al. 2016). The primary aim of the study was to investigate if gait variability increased and if dynamic balance control reduced when exertion levels were high. The study method employed did not adequately consider falls history or have adequate numbers to contrast COPD fallers with non-fallers.

Future recommendations

Comparison studies using different types of gait analysis

Future research should employ new technology in gait assessment and give comparisons between different phenotypes of COPD and stratifications of disease progression. Presently, there are no studies comparing gait variability response to exertion in COPD for fallers versus non-fallers, different COPD phenotypes, varying GOLD stratifications, in stable or exacerbation phase, or pre- to post-participation in pulmonary rehabilitation. A relatively new recommendation in COPD management is the early commencement of pulmonary rehabilitation following onset of an infective exacerbation (Puhan et al. 2016; Ryrso et al. 2018). Gait analysis as a fall's prediction tool could be employed to assess the effectiveness of such interventions. Control group studies of this nature may elucidate differences in gait adaptations to exertion and be enhanced with new technologies that more thoroughly assess gait variability. Three-dimensional gait analysis has been used to demonstrate that people with COPD have reduced stride and step lengths, along with increased gait variability, in comparison to healthy elderly (Liu et al. 2017). Three-dimensional gait analysis may also assist in identifying common gait impairments not identifiable in gait sensor mats, such as impairments at the hip, knee, or ankle level.

Different types of dynamic balance analysis

In this study, dynamic balance control was measured on a flat and firm surface which may not replicate true to life conditions that challenge balance systems. Alias and Justine (2014) measured dynamic stability in healthy adults using the Modified Clinical Test of Sensory Integration before and after completing a 6MWT. Their results showed that participants had a statistically significant reduction in balance on a soft surface but not a firm surface, and hypothesise that the change was due to reduced sensory integration post-exercise (Alias & Justine 2014). It is probable that the FR test performed in the current study was inadequate in identifying sensory changes that occurred in response to elevated exertion levels. Multiple balance measures, including BESTest, Berg balance scale, force plates, single leg stance and others have been used to evaluate dynamic balance in people with COPD (Beauchamp 2019; Beauchamp et al. 2010; Lopes et al. 2014) some of which have validated minimal clinically important differences for this population (Beauchamp et al. 2016). Future study should investigate which components of balance are most affected by exertion, and if the effect translates to increased falls risk.

Conclusions

Gait variability (stance time standard deviation) and dynamic balance (FR) did not deteriorate from either paced or un-paced exertional walking, nor did it worsen at peek exertion levels. Gait variability did not deteriorate in response to increased velocity and had no clear relationship with measures of exertion during the walking tests. The clinical implications of these results are that walking with increased exertion for functional assessment is not likely to increase gait variability, reduce balance control, or elevate the risk of an accidental fall from baseline levels in mild to moderate COPD in controlled conditions. Measuring spatiotemporal gait variation and exertion concurrently was utilised as a safe and viable method for investigating falls risk in the COPD population. Future research could use this same method to identify the effect exertion on gait variability and balance control in different subgroups of the COPD population, including fallers versus non-fallers, stable versus those in acute exacerbation, and pulmonary rehabilitation trained versus untrained. Future investigations would require larger data sets to substantiate findings and study aims should focus on both identifying people at risk of falling and the ability to evaluate the effectiveness of interventions used to mitigate falls risk factors.

BIBLIOGRAPHY

Abu Samah, Z, Mohd Nordin, NA, Shahar, S & Singh, DKA 2016, 'Can gait speed test be used as a falls risk screening tool in community dwelling older adults? A review', *Polish Annals of Medicine*, vol. 23, no. 1, pp. 61-67.

Afzal, S, Burge, AT, Lee, AL, Bondarenko, J & Holland, AE 2018, 'Should the 6-Minute Walk Test Be Stopped If Oxyhemoglobin Saturation Falls Below 80%?', *Archives of Physical Medicine and Rehabilitation*, vol. 99, no. 11, pp. 2370-2372.

Agustí, AGN, Noguera, A, Sauleda, J, Sala, E, Pons, J & Busquets, X 2003, 'Systemic effects of chronic obstructive pulmonary disease', *European Respiratory Journal*, vol. 21, no. 2, p. 347.

Alahmari, AD, Kowlessar, BS, Patel, ARC, Mackay, AJ, Allinson, JP, Wedzicha, JA & Donaldson, GC 2016, 'Physical activity and exercise capacity in patients with moderate COPD exacerbations', *European Respiratory Journal*, vol. 48, no. 2, pp. 340-349.

Alahmari, AD, Patel, AR, Kowlessar, BS, Mackay, AJ, Singh, R, Wedzicha, JA & Donaldson, GC 2014, 'Daily activity during stability and exacerbation of chronic obstructive pulmonary disease', *BMC Pulmonary Medicine*, vol. 14, no. 1, p. 98.

Albergoni, A, Hettinga, FJ, La Torre, A, Bonato, M & Sartor, F 2019, 'The Role of Technology in Adherence to Physical Activity Programs in Patients with Chronic Diseases Experiencing Fatigue: a Systematic Review', *Sports Med Open*, vol. 5, no. 1, p. 41.

Alias, HA & Justine, M 2014, 'The impact of a submaximal level of exercise on balance performance in older persons', *ScientificWorldJournal*, vol. 2014, p. 986252.

Ambrose, AF, Paul, G & Hausdorff, JM 2013, 'Risk factors for falls among older adults: A review of the literature', *Maturitas*, vol. 75, no. 1, pp. 51-61.

Andrianopoulos, V, Wouters, EF, Pinto-Plata, VM, Vanfleteren, LE, Bakke, PS, Franssen, FM, Agusti, A, MacNee, W, Rennard, SI, Tal-Singer, R, Vogiatzis, I, Vestbo, J, Celli, BR & Spruit, MA 2015, 'Prognostic value of variables derived from the six-minute walk test in patients with COPD: Results from the ECLIPSE study', *Respiratory Medicine*, vol. 109, no. 9, pp. 1138-1146.

Anecchino, C, Rossi, E, Fanizza, C, De Rosa, M, Tognoni, G, Romero, M, Andretta, M, Castellani, L, Cecchetto, M, De Cal, M, DiTuri, R, Gallo, R, Garibaldi, D, Grion, AM, Grossetti, M, La Bella, G, Lena, F, Maccari, D, Marinai, C, Moruzzo, M, Nava, E, Orsini, A, Pari, B, Pedrini, A, Rais, M, Rizzotti, G, Cariolato, MP & Zogno, MG 2007, 'Prevalence of chronic obstructive pulmonary disease and pattern of comorbidities in a general population', *International Journal of COPD*, vol. 2, no. 4, pp. 567-574.

Annegarn, J, Spruit, MA, Savelberg, HHCM, Willems, PJB, van de Bool, C, Schols, AMWJ, Wouters, EFM & Meijer, K 2012, 'Differences in walking pattern during 6-min walk test between patients with COPD and healthy subjects', *PloS One*, vol. 7, no. 5.

Arne, M, Janson, C, Janson, S, Boman, G, Lindqvist, U, Berne, C & Emtner, M 2009, 'Physical activity and quality of life in subjects with chronic disease: chronic obstructive pulmonary disease compared with rheumatoid arthritis and diabetes mellitus', *Scandinavian Journal of Primary Health Care*, vol. 27, no. 3, pp. 141-147.

Auvinet, B, Berrut, G, Touzard, C, Moutel, L, Collet, N, Chaleil, D & Barrey, E 2002, 'Reference data for normal subjects obtained with an accelerometric device', *Gait and Posture*, vol. 16, no. 2, pp. 124-134.

Ayiesah, R & Chang, YY 2010, 'Comparison of physiological responses to six minute walk test and incremental shuttle walk test among COPD patients in UKMMC', *Sains Malaysiana*, vol. 39, no. 5, pp. 863-868.

Beauchamp, MK 2019, 'Balance assessment in people with COPD: An evidence-based guide', *Chronic Respiratory Disease*, vol. 16, p. 1479973118820311.

Beauchamp, MK, Brooks, D & Goldstein, RS 2010, 'Deficits in postural control in individuals with COPD - emerging evidence for an important secondary impairment', *Multidiscip Respir Med*, vol. 5, no. 6, pp. 417-421.

Beauchamp, MK, Harrison, SL, Goldstein, RS & Brooks, D 2016, 'Interpretability of change scores in measures of balance in people with COPD', *Chest*, vol. 149, no. 3, pp. 696-703.

Beauchamp, MK, Hill, K, Goldstein, RS, Janaudis-Ferreira, T & Brooks, D 2009, 'Impairments in balance discriminate fallers from non-fallers in COPD', *Respiratory Medicine*, vol. 103, no. 12, pp. 1885-1891.

Beauchamp, MK, Janaudis-Ferreira, T, Parreira, V, Romano, JM, Woon, L, Goldstein, RS & Brooks, D 2013, 'A randomized controlled trial of balance training during pulmonary rehabilitation for individuals with COPD', *Chest*, vol. 144, no. 6, pp. 1803-1810.

Beauchamp, MK, O'Hoski, S, Goldstein, RS & Brooks, D 2010, 'Effect of pulmonary rehabilitation on balance in persons with chronic obstructive pulmonary disease', *Archives of Physical Medicine and Rehabilitation*, vol. 91, no. 9, pp. 1460-1465.

Beauchamp, MK, Sibley, KM, Lakhani, B, Romano, J, Mathur, S, Goldstein, RS & Brooks, D 2012, 'Impairments in systems underlying control of balance in COPD', *Chest*, vol. 141, no. 6, pp. 1496-1503.

Bhosle, P, Alaparthi, GK & Krishnan, S 2012, 'Functional balance in chronic obstructive pulmonary disease: a case control study', *International Journal of Health Sciences and Research*, vol. 2, no. 3, pp. 61-71.

Biskobing, DM 2002, 'COPD and Osteoporosis', *Chest*, vol. 121, no. 2, pp. 609-620.

Blondeel, A, Demeyer, H, Janssens, W & Troosters, T 2018, 'The role of physical activity in the context of pulmonary rehabilitation', *COPD*, vol. 15, no. 6, pp. 632-639.

Boccia, G, Dardanello, D, Rinaldo, N, Coratella, G, Schena, F & Rainoldi, A 2015, 'Electromyographic manifestations of fatigue correlate with pulmonary function, 6-minute walk test, and time to exhaustion in COPD', *Respiratory Care*, vol. 60, no. 9, pp. 1295-1302.

Bongue, B, Dupre, C, Beauchet, O, Rossat, A, Fantino, B & Colvez, A 2011, 'A screening tool with five risk factors was developed for fall-risk prediction in community-dwelling elderly', *Journal of Clinical Epidemiology*, vol. 64, no. 10, pp. 1152-1160.

Bousquet, J, Dinh-Xuan, AT, Similowski, T, Malva, J, Ankri, J, Barbagallo, M, Fabbri, L, Humbert, M, Mercier, J, Robalo-Cordeiro, C, Rodriguez-Manas, L & Vellas, B 2016, 'Should we use gait speed in COPD, FEV1 in frailty and dyspnoea in both?', *European Respiratory Journal*, vol. 48, no. 2, pp. 315-319.

Bozek, A, Jarzab, J, Hadas, E, Jakalski, M & Canonica, GW 2019, 'Fall episodes in elderly patients with asthma and COPD - A pilot study', *Journal of Asthma*, vol. 56, no. 6, pp. 627-631.

Brach, JS, Berlin, JE, VanSwearingen, JM, Newman, AB & Studenski, SA 2005, 'Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed', *Journal of Neuroengineering and Rehabilitation*, vol. 2, p. 21.

Brooke, M 2013, 'COPD and its management in Australia', *Journal of the Australasian Rehabilitation Nurses' Association (JARNA)*, vol. 16, no. 2, pp. 8-12.

Brown, CD & Wise, RA 2007, 'Field tests of exercise in COPD: The six-minute walk test and the shuttle walk test', *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 4, no. 3, pp. 217-223.

Callisaya, ML, Blizzard, L, Schmidt, MD, McGinley, JL & Srikanth, VK 2010, 'Ageing and gait variability-a population-based study of older people', *Age and Ageing*, vol. 39, no. 2, pp. 191-197.

Camp, PG, Reid, WD, Chung, F, Kirkham, A, Brooks, D, Goodridge, D, Marciniuk, DD & Hoens, AM 2015, 'Clinical Decision-Making Tool for Safe and Effective Prescription of Exercise in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Results From an Interdisciplinary Delphi Survey and Focus Groups', *Phys Ther*, vol. 95, no. 10, pp. 1387-1396.

Casey, G 2015, *Capnography: monitoring CO2*, New Zealand Nurses Organisation, 1173-2032, <https://login.ezproxy.utas.edu.au/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=110468564&site=eds-live>.

Celli, B, Tetzl, K, Criner, G, Polkey, MI, Sciurba, F, Casaburi, R, Tal-Singer, R, Kawata, A, Merrill, D & Rennard, S 2016, 'The 6-minute-walk distance test as a chronic obstructive pulmonary disease stratification tool insights from the COPD biomarker qualification consortium', *American Journal of Respiratory and Critical Care Medicine*, vol. 194, no. 12, pp. 1483-1493.

Charbek, E, Huynh, K, Kim, E & Nayak, RP 2019, 'Assessment of Cognitive Impairment in Patients with Chronic Obstructive Pulmonary Disease Using the Rapid Cognitive Screen', *Journal of Nutrition, Health and Aging*, vol. 23, no. 1, pp. 102-104.

Chen, S, Wu, Y-T, Lin, J-J, Lee, C-N, Huang, C-Y & Chiang, L-L 2012, 'The Correlations of the Six-minute Walk Test and Respiratory Functions in Chronic Obstructive Pulmonary Disease Patients with Chronic Hypercapnia', *Journal of Experimental & Clinical Medicine (18783317)*, vol. 4, no. 1, p. 47.

Copur, AS, Fulambarker, A, Molnar, J, Nadeem, R, McCormack, C, Ganesh, A, Kheir, F & Hamon, S 2015, 'Role of Anemia in Home Oxygen Therapy in Chronic Obstructive Pulmonary Disease Patients', *American Journal of Therapeutics*, vol. 22, no. 5, pp. 361-366.

Corsonello, A, Antonelli Incalzi, R, Pistelli, R, Pedone, C, Bustacchini, S & Lattanzio, F 2011, 'Comorbidities of chronic obstructive pulmonary disease', *Current Opinion in Pulmonary Medicine*, vol. 17, no. SUPPL. 1, pp. S21-S28.

Crisan, AF, Oancea, C, Timar, B, Fira-Mladinescu, O & Tudorache, V 2015, 'Balance impairment in patients with COPD', *PloS One*, vol. 10, no. 3, p. e0120573.

Cruz, J, Marques, A, Jácome, C, Gabriel, R & Figueiredo, D 2015, 'Global functioning of COPD patients with and without functional balance impairment: An exploratory analysis based on the ICF framework', *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 12, no. 2, pp. 207-216.

Da Rocha, ES, Kunzler, MR, Bobbert, MF, Duysens, J & Carpes, FP 2018, '30 min of treadmill walking at self-selected speed does not increase gait variability in independent elderly', *Journal of Sports Sciences*, vol. 36, no. 11, pp. 1305-1311.

Dajczman, E, Wardini, R, Kasymjanova, G, Préfontaine, D, Baltzan, MA & Wolkove, N 2015, 'Six minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation', *Canadian Respiratory Journal*, vol. 22, no. 4, pp. 225-229.

De Castro, LA, Ribeiro, LR, Mesquita, R, De Carvalho, DR, Felcar, JM, Merli, MF, Fernandes, KBP, Da Silva, RA, Teixeira, DC, Spruit, MA, Pitta, F & Probst, VS 2016, 'Static and functional balance in individuals with COPD: Comparison with healthy controls and differences according to sex and disease severity', *Respiratory Care*, vol. 61, no. 11, pp. 1488-1496.

de Miguel-Diez, J, Jiménez-García, R, Hernández-Barrera, V, Carrasco-Garrido, P, Puente-Maestu, L, Ramírez García, L & Lopez de Andres, A 2016, 'Is COPD a Risk Factor for Hip Fracture?', *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 13, no. 6, pp. 779-789.

De, P & Bhuniya, S 2015, 'The Rotterdam study: Why fall in COPD?', *European Respiratory Journal*, vol. 46, no. 5, pp. 1529-1530.

Delbaere, K, Close, JCT, Heim, J, Sachdev, PS, Brodaty, H, Slavin, MJ, Kochan, NA & Lord, SR 2010, 'A multifactorial approach to understanding fall risk in older people', *Journal of the American Geriatrics Society*, vol. 58, no. 9, pp. 1679-1685.

DeMeulenaere, S 2007, 'Pulse oximetry: uses and limitations.', *Journal for Nurse Practitioners*, vol. 3, no. 5, pp. 312-317.

Donath, L, Zahner, L, Roth, R, Fricker, L, Cordes, M, Hanssen, H, Schmidt-Trucksäss, A & Faude, O 2013, 'Balance and gait performance after maximal and submaximal endurance exercise in seniors: Is there a higher fall-risk?', *European Journal of Applied Physiology*, vol. 113, no. 3, pp. 661-669.

Duncan, PW, Studenski, S, Chandler, J & Prescott, B 1992, 'Functional Reach: Predictive Validity in a Sample of Elderly Male Veterans', *Journal of Gerontology*, vol. 47, no. 3, pp. M93-M98.

Duncan, PW, Weiner, DK, Chandler, J & Studenski, S 1990, 'Functional reach: a new clinical measure of balance', *Journal of Gerontology*, vol. 45, no. 6, pp. M192-M197.

Eisner, MD, Blanc, PD, Yelin, EH, Sidney, S, Katz, PP, Ackerson, L, Lathon, P, Tolstykh, I, Omachi, T, Byl, N & Iribarren, C 2008, 'COPD as a Systemic Disease: Impact on Physical Functional Limitations', *American Journal of Medicine*, vol. 121, no. 9, pp. 789-796.

Gazzotti, MR, Roco, CM, Pradella, CO, Nascimento, OA, Porto, EF, Adas, M, Lazaretti-Castro, M & Jardim, JR 2019, 'Frequency of Osteoporosis and Vertebral Fractures in Chronic Obstructive Pulmonary Disease (COPD) Patients', *Archivos de Bronconeumología (English Edition)*, vol. 55, no. 5, pp. 252-257.

Gillain, S, Boutaayamou, M, Beaudart, C, Demonceau, M, Bruyère, O, Reginster, JY, Garraux, G & Petermans, J 2018, 'Assessing gait parameters with accelerometer-based methods to identify older adults at risk of falls: a systematic review', *European Geriatric Medicine*, vol. 9, no. 4, pp. 435-448.

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 REPORT, Global Initiative for Chronic Obstructive Lung Disease, Inc., viewed 14/04/2020, <https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf.>.

Gloeckl, R, Marinov, B & Pitta, F 2013, 'Practical recommendations for exercise training in patients with COPD', *European Respiratory Review*, vol. 22, no. 128, pp. 178-186.

Graat-Verboom, L, Wouters, EFM, Smeen, FWJM, Van Den Borne, BEEM, Lunde, R & Spruit, MA 2009, 'Current status of research on osteoporosis in COPD: A systematic review', *European Respiratory Journal*, vol. 34, no. 1, pp. 209-218.

Graat-Verboom, L, Wouters, EFM, Smeenk, FWJM, van den Borne, BEEM, Lunde, R & Spruit, MA 2009, 'Current status of research on osteoporosis in COPD: a systematic review', *European Respiratory Journal*, vol. 34, no. 1, p. 209.

Gregg, EW, Pereira, MA & Caspersen, CJ 2000, 'Physical activity, falls, and fractures among older adults: A review of the epidemiologic evidence', *Journal of the American Geriatrics Society*, vol. 48, no. 8, pp. 883-893.

Guyatt, GH, Pugsley, SO, Sullivan, MJ, Thompson, P, Berman, L, Jones, N, Fallen, E & Taylor, DW 1984, 'Effect of encouragement on walking test performance', *Thorax*, vol. 39, no. 11, pp. 818-822.

Guyatt, GH, Sullivan, MJ, Thompson, PJ, Fallen, EL, Pugsley, SO, Taylor, DW & Berman, LB 1985, 'The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure', *Canadian Medical Association Journal*, vol. 132, no. 8, p. 919.

Hakamy, A, Bolton, CE, Gibson, JE & McKeever, TM 2018, 'Risk of fall in patients with COPD', *Thorax*, vol. 73, no. 11, pp. 1079-1080.

Hakamy, A, Bolton, CE & McKeever, TM 2017, 'The effect of pulmonary rehabilitation on mortality, balance, and risk of fall in stable patients with chronic obstructive pulmonary disease', *Chronic Respiratory Disease*, vol. 14, no. 1, pp. 54-62.

Hakemi, A & Bender, JA 2005, 'Understanding pulse oximetry, advantages, and limitations', *Home Health Care Management and Practice*, vol. 17, no. 5, pp. 416-418.

Halbert, RJ, Natoli, JL, Gano, A, Badamgarav, E, Buist, AS & Mannino, DM 2006, 'Global burden of COPD: systematic review and meta-analysis', *European Respiratory Journal*, vol. 28, no. 3, p. 523.

Hanlon, P, Nicholl, BI, Jani, BD, McQueenie, R, Lee, D, Gallacher, KI & Mair, FS 2018, 'Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: a cross-sectional UK Biobank study', *BMJ Open*, vol. 8, no. 1, p. e018404.

Harrison, SL, Araujo, T, Goldstein, R & Brooks, D 2019, 'Balance Measures over 12 Months in Individuals with Chronic Obstructive Pulmonary Disease', *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 39, no. 3, pp. E21-E24.

Hausdorff, JM, Rios, DA & Edelberg, HK 2001, 'Gait variability and fall risk in community-living older adults: A 1-year prospective study', *Archives of Physical Medicine and Rehabilitation*, vol. 82, no. 8, pp. 1050-1056.

Hellstrom, K, Vahlberg, B, Urell, C & Emtner, M 2009, 'Fear of falling, fall-related self-efficacy, anxiety and depression in individuals with chronic obstructive pulmonary disease', *Clinical Rehabilitation*, vol. 23, no. 12, pp. 1136-1144.

Heraud, N, Alexandre, F, Gueugnon, M, Davy, C, Tremey, E, Oliver, N & Varray, A 2018, 'Impact of Chronic Obstructive Pulmonary Disease on Cognitive and Motor Performances in Dual-Task Walking', *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 15, no. 3, pp. 277-282.

Hill, K 2014, 'Balance-specific training embedded within a pulmonary rehabilitation program may reduce falls risk in people with COPD', *Journal of Physiotherapy*, vol. 60, no. 2, p. 111.

Hill, K, Dolmage, TE, Woon, L, Coutts, D, Goldstein, R & Brooks, D 2012, 'Comparing peak and submaximal cardiorespiratory responses during field walking tests with incremental cycle ergometry in COPD', *Respirology*, vol. 17, no. 2, pp. 278-284.

Ho, CF & Maa, SH 2016, 'Application of the 6-minute walking test and shuttle walking test in the exercise tests of patients with COPD', *Journal of Nursing*, vol. 63, no. 4, pp. 107-115.

Hodgev, VA, Aliman, OI, Marinov, BI, Kostianev, SS & Mandulova, PV 2003, 'Cardiovascular and dyspnea response to six-minute and shuttle walk tests in COPD patients', *Folia medica*, vol. 45, no. 3, pp. 26-33.

Holland, AE, Harrison, SL & Brooks, D 2016, 'Multimorbidity, frailty and chronic obstructive pulmonary disease: Are the challenges for pulmonary rehabilitation in the name?', *Chronic Respiratory Disease*, vol. 13, no. 4, pp. 372-382.

Holland, AE, Spruit, MA, Troosters, T, Puhan, MA, Pepin, V, Saey, D, McCormack, MC, Carlin, BW, Sciurba, FC & Pitta, F 2014, *An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease*, Eur Respiratory Soc, 0903-1936.

Horie, J, Anami, K, Imaizumi, Y, Ichimaru, K, Naotsuka, H, Shiranita, S, Tanaka, M, Hayashi, SI & Horikawa, E 2011, 'Examination of the difference in balance ability across the disease stages of male chronic obstructive pulmonary disease patients', *Rigakuryoho Kagaku*, vol. 26, no. 2, pp. 215-219.

Huang, S-W, Wang, W-T, Chou, L-C, Chen, H-C, Liou, T-H & Lin, H-W 2016, 'Chronic Obstructive Pulmonary Disease Increases the Risk of Hip Fracture: A Nationwide Population-Based Cohort Study', *Scientific Reports*, vol. 6, p. 23360.

Ilgin, D, Ozalevli, S, Kilinc, O, Sevinc, C, Cimrin, AH & Ucan, ES 2011, 'Gait speed as a functional capacity indicator in patients with chronic obstructive pulmonary disease', *Annals of Thoracic Medicine*, vol. 6, no. 3, pp. 141-146.

Isles, RC, Low Choy, NL, Steer, M & Nitz, JC 2004, 'Normal values of balance tests in women aged 20-80', *Journal of the American Geriatrics Society*, vol. 52, no. 8, pp. 1367-1372.

Iwakura, M, Okura, K, Shibata, K, Kawagoshi, A, Sugawara, K, Takahashi, H, Shioya, T & Wakasa, M 2019, 'Gait characteristics and their associations with clinical outcomes in patients with chronic obstructive pulmonary disease', *Gait and Posture*, vol. 74, pp. 60-65.

Jacome, C, Cruz, J, Gabriel, R, Figueiredo, D & Marques, A 2014, 'Functional Balance in Older Adults With Chronic Obstructive Pulmonary Disease', *Journal of Aging and Physical Activity*, vol. 22, no. 3, pp. 357-363.

Jácome, C, Cruz, J, Oliveira, A & Marques, A 2016, 'Validity, Reliability, and Ability to Identify Fall Status of the Berg Balance Scale, BESTest, Mini-BESTest, and Brief-BESTest in Patients With COPD', *Physical Therapy*, vol. 96, no. 11, pp. 1807-1815.

Janssens, L, Brumagne, S, McConnell, AK, Claeys, K, Pijnenburg, M, Goossens, N, Burtin, C, Janssens, W, Decramer, M & Troosters, T 2014, 'Impaired postural control reduces sit-to-stand-to-sit performance in individuals with chronic obstructive pulmonary disease', *PloS One*, vol. 9, no. 2, p. e88247.

Jaramillo, JD, Wilson, C, Stinson, DJ, Lynch, DA, Bowler, RP, Lutz, S, Bon, JM, Arnold, B, McDonald, M-LN, Washko, GR, Wan, ES, DeMeo, DL, Foreman, MG, Soler, X, Lindsay, SE, Lane, NE, Genant, HK, Silverman, EK, Hokanson, JE, Make, BJ, Crapo, JD & Regan, EA 2015, 'Reduced Bone Density and Vertebral Fractures in Smokers. Men and COPD Patients at Increased Risk', *Annals of the American Thoracic Society*, vol. 12, no. 5, pp. 648-656.

Jenkins, S & Čečins, N 2011, 'Six-minute walk test: Observed adverse events and oxygen desaturation in a large cohort of patients with chronic lung disease', *Internal Medicine Journal*, vol. 41, no. 5, pp. 416-422.

Jenkins, SC 2007, '6-Minute walk test in patients with COPD: clinical applications in pulmonary rehabilitation', *Physiotherapy*, vol. 93, no. 3, pp. 175-182.

Jensen, LA, Onyskiw, JE & Prasad, NGN 1998, 'Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults', *Heart and Lung: Journal of Acute and Critical Care*, vol. 27, no. 6, pp. 387-408.

Jorgensen, TSH, Holm, E, Hansen, AH, Sahlberg, M, Gislason, GH, Torp Pedersen, C & Andersson, C 2014, 'Falls and comorbidity: The pathway to fractures', *Scandinavian Journal of Public Health*, vol. 42, no. 3, pp. 287-294.

Karpman, C & Benzo, R 2014, 'Gait speed as a measure of functional status in COPD patients', *International Journal of COPD*, vol. 9, pp. 1315-1320.

Kim, V & Aaron, SD 2018, 'What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement', *European Respiratory Journal*, vol. 52, no. 5, p. 1801261.

Lahousse, L, Verlinden, VJ, van der Geest, JN, Joos, GF, Hofman, A, Stricker, BH, Brusselle, GG & Ikram, MA 2015, 'Gait patterns in COPD: the Rotterdam Study', *European Respiratory Journal*, vol. 46, no. 1, pp. 88-95.

Landis, SH, Muellerova, H, Mannino, DM, Menezes, AM, Han, MK, van der Molen, T, Ichinose, M, Aisanov, Z, Oh, YM & Davis, KJ 2014, 'Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012-2013', *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 9, pp. 597-611.

Lawi, D, Berra, G, Janssens, JP, Soccal, PM & Adler, D 2018, 'COPD and cognitive impairment', *Revue Medicale Suisse*, vol. 14, no. 627, pp. 2066-2069.

Lawlor, DA, Patel, R & Ebrahim, S 2003a, 'Association between falls in elderly women and chronic diseases and drug use: cross sectional study', *BMJ*, vol. 327, no. 7417, pp. 712-717.

Lawlor, DA, Patel, R & Ebrahim, S 2003b, 'Association between falls in elderly women and chronic diseases and drug use: cross sectional study', *British Medical Journal*, vol. 327, no. 7417, pp. 712-715.

Lisspers, K, Larsson, K, Johansson, G, Janson, C, Costa-Scharplatz, M, Gruenberger, JB, Uhde, M, Jorgensen, L, Gutzwiller, FS & Stallberg, B 2018, 'Economic burden of COPD in a Swedish cohort: the ARCTIC study', *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 13, pp. 275-285.

Lisy, K, White, H & Pearson, A 2014, 'Overview of reviews: Mechanical interventions for the treatment and management of chronic obstructive pulmonary disease', *International Journal of Nursing Practice*, vol. 20, no. 6, pp. 701-708.

Liu, WY, Spruit, MA, Delbressine, JM, Willems, PJ, Franssen, FME, Wouters, EFM & Meijer, K 2017, 'Spatiotemporal gait characteristics in patients with COPD during the Gait Real-time Analysis Interactive Lab-based 6-minute walk test', *PloS One*, vol. 12, no. 12, p. e0190099.

Lopes, AJ, Pinto Almeida, V, Silveira Menezes, SL & Guimaraes, FS 2014, 'Balance Deficits are Correlated with Bronchial Obstruction Markers in Subjects with Asthma', *Journal of physical therapy science*, vol. 26, no. 3, pp. 393-399.

Lozano, R, Naghavi, M, Foreman, K, Lim, S, Shibuya, K, Aboyans, V, Abraham, J, Adair, T, Aggarwal, R & Ahn, SY 2012, 'Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010', *The Lancet*, vol. 380, no. 9859, pp. 2095-2128.

Lu, PC, Yang, YH, Guo, SE & Yang, TM 2017, 'Factors associated with osteoporosis in patients with chronic obstructive pulmonary disease—a nationwide retrospective study', *Osteoporosis International*, vol. 28, no. 1, pp. 359-367.

Luxton, N, Alison, JA, Wu, J & Mackey, MG 2008, 'Relationship between field walking tests and incremental cycle ergometry in COPD', *Respirology*, vol. 13, no. 6, pp. 856-862.

Marques, A, Jácome, C, Cruz, J, Gabriel, R & Figueiredo, D 2015, 'Effects of a Pulmonary Rehabilitation Program with Balance Training on Patients with COPD', *Journal Of Cardiopulmonary Rehabilitation And Prevention*, vol. 35, no. 2, pp. 154-158.

Marques, NR, Hallal, CZ, Spinoso, DH, Morcelli, MH, Crozara, LF & Gonçalves, M 2017, 'Applying different mathematical variability methods to identify older fallers and non-fallers using gait variability data', *Aging Clinical and Experimental Research*, vol. 29, no. 3, pp. 473-481.

Marques, NR, Spinoso, DH, Cardoso, BC, Moreno, VC, Kuroda, MH & Navega, MT 2018, 'Is it possible to predict falls in older adults using gait kinematics?', *Clinical Biomechanics*, vol. 59, pp. 15-18.

Marquis, N, Debigare, R, Bouyer, L, Saey, D, Laviolette, L, Brouillard, C & Maltais, F 2009, 'Physiology of walking in patients with moderate to severe chronic obstructive pulmonary disease', *Medicine and Science in Sports and Exercise*, vol. 41, no. 8, pp. 1540-1548.

Masnoon, N, Shakib, S, Kalisch-Ellett, L & Caughey, GE 2017, 'What is polypharmacy? A systematic review of definitions', *BMC Geriatrics*, vol. 17, no. 1, p. 230.

Massery, M 2009, 'The linda crane memorial lecture: The Patient Puzzle: Piecing it Together', *Cardiopulmonary Physical Therapy Journal*, vol. 20, no. 2, p. 19.

Mathers, CD & Loncar, D 2006, 'Projections of global mortality and burden of disease from 2002 to 2030', *PLoS Medicine*, vol. 3, no. 11, pp. 2011-2030.

McCarthy, B, Casey, D, Devane, D, Murphy, K, Murphy, E & Lacasse, Y 2015, 'Pulmonary rehabilitation for chronic obstructive pulmonary disease', *Cochrane Database of Systematic Reviews*, vol. 2, no. 2, p. CD003793.

McDonough, AL, Batavia, M, Chen, FC, Kwon, S & Ziai, J 2001, 'The validity and reliability of the GAITRite system's measurements: A preliminary evaluation', *Archives of Physical Medicine and Rehabilitation*, vol. 82, no. 3, pp. 419-425.

Medeiros, WM, Fernandes, MC, Azevedo, DP, de Freitas, FF, Amorim, BC, Chiavegato, LD, Hirai, DM, O'Donnell, DE & Neder, JA 2014, 'Oxygen delivery-utilization mismatch in contracting locomotor muscle in COPD: peripheral factors', *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 308, no. 2, pp. R105-R111.

Mercado, N, Ito, K & Barnes, PJ 2015, 'Accelerated ageing of the lung in COPD: new concepts', *Thorax*, vol. 70, no. 5, pp. 482-489.

Mignardot, JB, Deschamps, T, Barrey, E, Auvinet, B, Berrut, G, Cornu, C, Constans, T & de Decker, L 2014, 'Gait disturbances as specific predictive markers of the first fall onset in elderly people: a two-year prospective observational study', *Frontiers in Aging Neuroscience*, vol. 6, p. 22.

Ming-Lung, C, Lin, IF & Shih-Pin, C 2014, 'Kinetics of Changes in Oxyhemoglobin Saturation During Walking and Cycling Tests in COPD', *Respiratory Care*, vol. 59, no. 3, pp. 353-362.

Mirza, S, Clay, RD, Koslow, MA & Scanlon, PD 2018, 'COPD Guidelines: A Review of the 2018 GOLD Report', *Mayo Clinic Proceedings*, vol. 93, no. 10, pp. 1488-1502.

Misof, BM, Moreira, CA, Klaushofer, K & Roschger, P 2016, 'Skeletal Implications of Chronic Obstructive Pulmonary Disease', *Current Osteoporosis Reports*, vol. 14, no. 2, pp. 49-53.

Mittal, N, Raj, R, Islam, EA & Nugent, K 2016, 'The Frequency of Frailty in Ambulatory Patients With Chronic Lung Diseases', *Journal of Primary Care & Community Health*, vol. 7, no. 1, pp. 10-15.

Mkacher, W, Mekki, M, Tabka, Z & Trabelsi, Y 2015, 'Effect of 6 Months of Balance Training during Pulmonary Rehabilitation in Patients with COPD', *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 35, no. 3, pp. 207-213.

Moe-Nilssen, R 1998, 'A new method for evaluating motor control in gait under real-life environmental conditions. Part 2: Gait analysis', *Clinical Biomechanics (Bristol, Avon)*, vol. 13, no. 4-5, pp. 328-335.

Morlino, P, Balbi, B, Guglielmetti, S, Giardini, M, Grasso, M, Giordano, C, Schieppati, M & Nardone, A 2017, 'Gait abnormalities of COPD are not directly related to respiratory function', *Gait and Posture*, vol. 58, pp. 352-357.

Mortaza, N, Abu Osman, NA & Mehdikhani, N 2014, 'Are the spatio-temporal parameters of gait capable of distinguishing a faller from a non-faller elderly?', *European Journal of Physical and Rehabilitation Medicine*, vol. 50, no. 6, pp. 677-691.

Motulsky, DH, *Graph Pad Software*, viewed 01/11/2016, <http://www.graphpad.com/quickcalcs/randMenu/>.

Muir, SW, Beauchet, O, Montero-Odasso, M, Annweiler, C, Fantino, B & Speechley, M 2013, 'Association of executive function impairment, history of falls and physical performance in older adults: a cross-sectional population-based study in eastern France', *The Journal of Nutrition, Health & Aging*, vol. 17, no. 8, pp. 661-665.

Muir, SW, Gopaul, K & Montero Odasso, MM 2012, 'The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis', *Age and Ageing*, vol. 41, no. 3, pp. 299-308.

Mukundu, L 2015, 'Managing COPD using pulmonary rehabilitation: a literature review', *Nursing Standard*, vol. 30, no. 14, pp. 38-43.

Nagano, H, James, L, Sparrow, WA & Begg, RK 2014, 'Effects of walking-induced fatigue on gait function and tripping risks in older adults', *Journal of Neuroengineering and Rehabilitation*, vol. 11, no. 1, p. 155.

Nantsupawat, N, Lane, P, Siangpraipunt, O, Gadwala, S & Nugent, K 2015, 'Gait Characteristics in Patients With Chronic Obstructive Pulmonary Disease', *Journal of Primary Care & Community Health*, vol. 6, no. 4, pp. 222-226.

Neumannová, K, Svoboda, Z, Zatloukal, J, Sedlák, V, Plutinský, M, Bizovská, L, Janura, M & Koblížek, V 2017, 'Balance disorders in patients with chronic obstructive pulmonary disease', *Studia Pneumologica et Phthiseologica*, vol. 77, no. 3, pp. 110-114.

Oliveira, CC, Lee, A, Granger, CL, Miller, KJ, Irving, LB & Denehy, L 2013, 'Postural control and fear of falling assessment in people with chronic obstructive pulmonary disease: a systematic review of instruments, international classification of functioning, disability and health linkage, and measurement properties', *Archives of Physical Medicine and Rehabilitation*, vol. 94, no. 9, pp. 1784-1799. e1787.

Oliveira, CC, Lee, AL, McGinley, J, Anderson, GP, Clark, RA, Thompson, M, Clarke, S, Baker, T, Irving, LB & Denehy, L 2017, 'Balance and Falls in Acute Exacerbation of Chronic Obstructive Pulmonary

Disease: A Prospective Study', *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 14, no. 5, pp. 518-525.

Oliveira, CC, Lee, AL, McGinley, J, Thompson, M, Irving, LB, Anderson, GP, Clark, RA, Clarke, S & Denehy, L 2015, 'Falls by individuals with chronic obstructive pulmonary disease: A preliminary 12-month prospective cohort study', *Respirology*, vol. 20, no. 7, pp. 1096-1101.

Onorati, P, Antonucci, R, Valli, G, Berton, E, De Marco, F, Serra, P & Palange, P 2003, 'Non-invasive evaluation of gas exchange during a shuttle walking test vs. a 6-min walking test to assess exercise tolerance in COPD patients', *European Journal of Applied Physiology*, vol. 89, no. 3-4, pp. 331-336.

Ozalevli, S, Ilgin, D, Narin, S & Akkoclu, A 2011, 'Association between disease-related factors and balance and falls among the elderly with COPD: A cross-sectional study', *Aging Clinical and Experimental Research*, vol. 23, no. 5-6, pp. 372-377.

Paliwal, Y, Slattum, PW & Ratliff, SM 2017, 'Chronic Health Conditions as a Risk Factor for Falls among the Community-Dwelling US Older Adults: A Zero-Inflated Regression Modeling Approach', *Biomed Research International*, p. 9.

Panagioti, M, Scott, C, Blakemore, A & Coventry, PA 2014, 'Overview of the prevalence, impact, and management of depression and anxiety in chronic obstructive pulmonary disease', *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 9, pp. 1289-1306.

Park, H, Satoh, H, Miki, A, Urushihara, H & Sawada, Y 2015, 'Medications associated with falls in older people: systematic review of publications from a recent 5-year period', *European Journal of Clinical Pharmacology*, vol. 71, no. 12, pp. 1429-1440.

Pichon, R, Beaumont, M, Peran, L & Le Ber-Moy, C 2012, 'Effects of a pulmonary rehabilitation program on the balance of patients with COPD', *Kinesitherapie*, vol. 12, no. 127, pp. 78-84.

Pollok, J, van Agteren, JE & Carson-Chahhoud, KV 2018, 'Pharmacological interventions for the treatment of depression in chronic obstructive pulmonary disease', *Cochrane Database of Systematic Reviews*, vol. 12, no. 12, p. CD012346.

Porto, EF, Castro, AAM, Schmidt, VGS, Rabelo, HM, Kümpel, C, Nascimento, OA & Jardim, JR 2015, 'Postural control in chronic obstructive pulmonary disease: A systematic review', *International Journal of COPD*, vol. 10, pp. 1233-1239.

Porto, EF, Pradella, CO, Rocco, CM, Chueiro, M, Maia, RQ, Gananca, FF, Castro, AAM, Nascimento, OA & Jardim, JR 2017, 'Comparative postural control in COPD patients and healthy individuals during dynamic and static activities', *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 37, no. 2, pp. 139-145.

Puhan, MA, Gimeno-Santos, E, Cates, CJ & Troosters, T 2016, 'Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease', *Cochrane Database of Systematic Reviews*, vol. 12, no. 12, p. CD005305.

Ramon, MA, Ter Riet, G, Carsin, AE, Gimeno-Santos, E, Agusti, A, Anto, JM, Donaire-Gonzalez, D, Ferrer, J, Rodriguez, E, Rodriguez-Roisin, R, Puhan, MA, Garcia-Aymerich, J & Group, P-CS 2018, 'The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model', *European Respiratory Journal*, vol. 52, no. 3, p. 1800079.

Randeep, M, Archana, D, Malay, S & Anita, P 2019, 'Cognitive Domain Impaired In COPD Patients And Its Correlation With Exercise Capacity In COPD Patients', *RESEARCH JOURNAL OF PHARMACEUTICAL BIOLOGICAL AND CHEMICAL SCIENCES*, vol. 10, no. 1, pp. 1132-1137.

Rennard, S, Decramer, M, Calverley, PMA, Pride, NB, Soriano, JB, Vermeire, PA & Vestbo, J 2002, 'Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey', *European Respiratory Journal*, vol. 20, no. 4, pp. 799-805.

Ries, AL 2005, 'Minimally Clinically Important Difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale', *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 2, no. 1, pp. 105-110.

Roig, M, Eng, JJ, MacIntyre, DL, Road, JD, FitzGerald, JM, Burns, J & Reid, WD 2011, 'Falls in people with chronic obstructive pulmonary disease: an observational cohort study', *Respiratory Medicine*, vol. 105, no. 3, pp. 461-469.

Roig, M, Eng, JJ, Road, JD & Reid, WD 2009, 'Falls in patients with chronic obstructive pulmonary disease: a call for further research', *Respiratory Medicine*, vol. 103, no. 9, pp. 1257-1269.

Romme, EA, Geusens, P, Lems, WF, Rutten, EP, Smeenk, FW, van den Bergh, JP, van Hal, PT & Wouters, EF 2015, 'Fracture prevention in COPD patients; a clinical 5-step approach', *Respiratory Research*, vol. 16, no. 1, p. 32.

Rosa, MV, Perracini, MR & Ricci, NA 2019, 'Usefulness, assessment and normative data of the Functional Reach Test in older adults: A systematic review and meta-analysis', *Archives of Gerontology and Geriatrics*, vol. 81, pp. 149-170.

Rutkowski, S, Rutkowska, A, Łuniewski, J & Szczegielniak, J 2014, 'Gait analysis of patients with chronic obstructive pulmonary disease', *Fizjoterapia Polska*, vol. 14, no. 4, pp. 24-33.

Ryrso, CK, Godtfredsen, NS, Kofod, LM, Lavesen, M, Mogensen, L, Tobberup, R, Farver-Vestergaard, I, Callesen, HE, Tendal, B, Lange, P & Iepsen, UW 2018, 'Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis', *BMC Pulmonary Medicine*, vol. 18, no. 1, p. 154.

Sanseverino, MA, Pecchiari, M, Bona, RL, Berton, DC, de Queiroz, FB, Gruet, M & Peyre-Tartaruga, LA 2018, 'Limiting Factors in Walking Performance of Subjects With COPD', *Respiratory Care*, vol. 63, no. 3, pp. 301-310.

Saunders, T, Campbell, N, Jason, T, Dechman, G, Hernandez, P, Thompson, K & Blanchard, CM 2016, 'Objectively measured steps/day in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis', *Journal of Physical Activity and Health*, vol. 13, no. 11, pp. 1275-1283.

Shumway-Cook, A & Woollacott, MH 2007, *Motor control: translating research into clinical practice*, Lippincott Williams & Wilkins.

Simard, AA, Maltais, F & LeBlanc, P 1995, 'Functional outcome of patients with chronic obstructive pulmonary disease and exercise hypercapnia', *The European respiratory journal*, vol. 8, no. 8, pp. 1339-1344.

Singh, SJ, Morgan, MD, Scott, S, Walters, D & Hardman, AE 1992, 'Development of a shuttle walking test of disability in patients with chronic airways obstruction', *Thorax*, vol. 47, no. 12, pp. 1019-1024.

Singh, SJ, Puhan, MA, Andrianopoulos, V, Hernandes, NA, Mitchell, KE, Hill, CJ, Lee, AL, Camillo, CA, Troosters, T, Spruit, MA, Carlin, BW, Wanger, J, Pepin, V, Saey, D, Pitta, F, Kaminsky, DA, McCormack, MC, MacIntyre, N, Culver, BH, Sciurba, FC, Revill, SM, Delafosse, V & Holland, AE 2014, 'An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease', *European Respiratory Journal*, vol. 44, no. 6, pp. 1447-1478.

Smith, RN & Hofmeyr, R 2019, 'Perioperative comparison of the agreement between a portable fingertip pulse oximeter v. A conventional bedside pulse oximeter in adult patients (COMFORT trial)', *South African Medical Journal*, vol. 109, no. 3, pp. 154-158.

Soriano, JB, Abajobir, AA, Abate, KH, Abera, SF, Agrawal, A, Ahmed, MB, Aichour, AN, Aichour, I, Aichour, MTE, Alam, K, Alam, N, Alkaabi, JM, Al-Maskari, F, Alvis-Guzman, N, Amberbir, A, Amoako, YA, Ansha, MG, Anto, JM, Asayesh, H, Atey, TM, Avokpaho, EFGA, Barac, A, Basu, S, Bedi, N, Bensenor, IM, Berhane, A, Beyene, AS, Bhutta, ZA, Biryukov, S, Boneya, DJ, Brauer, M, Carpenter, DO, Casey, D, Christopher, DJ, Dandona, L, Dandona, R, Dharmaratne, SD, Do, HP, Fischer, F, Geleto, A, Ghoshal, AG, Gillum, RF, Ginawi, IAM, Gupta, V, Hay, SI, Hedayati, MT, Horita, N, Hosgood, HD, Jakovljevic, MB, James, SL, Jonas, JB, Kasaeian, A, Khader, YS, Khalil, IA, Khan, EA, Khang, YH, Khubchandani, J, Knibbs, LD, Kosen, S, Koul, PA, Kumar, GA, Leshargie, CT, Liang, XF, Abd El Razek, HM, Majeed, A, Malta, DC, Manhertz, T, Marquez, N, Mehari, A, Mensah, GA, Miller, TR, Mohammad, KA, Mohammed, KE, Mohammed, S, Mokdad, AH, Naghavi, M, Nguyen, CT, Nguyen, G, Nguyen, QL, Nguyen, TH, Ningrum, DNA, Nong, VM, Obi, JI, Odeyemi, YE, Ogbo, FA, Oren, E, Mahesh, PA, Park, EK, Patton, GC, Paulson, K, Qorbani, M, Quansah, R, Rafay, A, Rahman, MHU, Rai, RK, Rawaf, S, Reinig, N, Safiri, S, Sarmiento-Suarez, R, Sartorius, B, Savic, M, Sawhney, M, Shigematsu, M, Smith, M, Tadese, F, Thurston, GD, Topor-Madry, R, Tran, BX, Ukwaja, KN, van Boven, JFM, Vlassov, VV, Vollset, SE, Wan, X, Werdecker, A, Hanson, SW, Yano, Y, Yimam, HH, Yonemoto, N, Yu, CH, Zaidi, Z, Zaki, ME, Murray, CJL, Vos, T & Collabor, GCRD 2017, 'Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015', *Lancet Respiratory Medicine*, vol. 5, no. 9, pp. 691-706.

Sousa, LM, Marques-Vieira, CM, Caldevilla, MN, Henriques, CM, Severino, SS & Caldeira, SM 2017, 'Risk for falls among community-dwelling older people: systematic literature review', *Revista Gaúcha de Enfermagem*, vol. 37, no. 4, p. e55030.

Souza, GF, Moreira, GL, Tufanin, A, Gazzotti, MR, Castro, AA, Jardim, JR & Nascimento, OA 2018, 'Physiological requirements to perform the glittre activities of daily living test by subjects with mild-to-severe COPD', *Respiratory Care*, vol. 62, no. 8, pp. 1049-1057.

Spruit, MA, Singh, SJ, Garvey, C, ZuWallack, R, Nici, L, Rochester, C, Hill, K, Holland, AE, Lareau, SC & Man, WD-C 2013, 'An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation', *American Journal of Respiratory and Critical Care Medicine*, vol. 188, no. 8, pp. e13-e64.

'Statistical Power Analysis for the Behavioral-Sciences - Cohen,J', 1988, *Perceptual and Motor Skills*, vol. 67, no. 3, pp. 1007-1007.

Steffen, TM, Hacker, TA & Mollinger, L 2002, 'Age-and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds', *Physical Therapy*, vol. 82, no. 2, pp. 128-137.

Studenski, S, Perera, S, Patel, K, Rosano, C, Faulkner, K, Inzitari, M, Brach, J, Chandler, J, Cawthon, P, Connor, EB, Nevitt, M, Visser, M, Kritchevsky, S, Badinelli, S, Harris, T, Newman, AB, Cauley, J, Ferrucci, L & Guralnik, J 2011, 'Gait speed and survival in older adults', *JAMA*, vol. 305, no. 1, pp. 50-58.

Tchalla, AE, Dufour, AB, Travison, TG, Habtemariam, D, Iloputaife, I, Manor, B & Lipsitz, LA 2014, 'Patterns, predictors, and outcomes of falls trajectories in older adults: the MOBILIZE Boston Study with 5 years of follow-up', *PloS One*, vol. 9, no. 9, p. e106363.

Tromp, AM, Pluijm, SM, Smit, JH, Deeg, DJ, Bouter, LM & Lips, P 2001, 'Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly', *Journal of Clinical Epidemiology*, vol. 54, no. 8, pp. 837-844.

Turner, SE, Eastwood, PR, Cecins, NM, Hillman, DR & Jenkins, SC 2004, 'Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests', *Chest*, vol. 126, no. 3, pp. 766-773.

van Beers, M, Janssen, DJA, Gosker, HR & Schols, AMWJ 2018, 'Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions', *Expert Review of Respiratory Medicine*, vol. 12, no. 12, pp. 1061-1074.

Vanfleteren, LEGW, Spruit, MA, Groenen, M, Gaffron, S, Van Empel, VPM, Bruijnzeel, PLB, Rutten, EPA, Roodt, JO, Wouters, EFM & Franssen, FME 2013, 'Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease', *American Journal of Respiratory and Critical Care Medicine*, vol. 187, no. 7, pp. 728-735.

Verghese, J, Holtzer, R, Lipton, RB & Wang, C 2009, 'Quantitative gait markers and incident fall risk in older adults', *The Journals of Gerontology: Series A*, vol. 64, no. 8, pp. 896-901.

Vespasiani-Gentilucci, U, Pedone, C, Muley-Vilamu, M & Antonelli-Incalzi, R 2018, 'The pharmacological treatment of chronic comorbidities in COPD: mind the gap!', *Pulmonary Pharmacology and Therapeutics*, vol. 51, pp. 48-58.

Vestbo, J, Hurd, SS, Agustí, AG, Jones, PW, Vogelmeier, C, Anzueto, A, Barnes, PJ, Fabbri, LM, Martinez, FJ & Nishimura, M 2013, 'Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary', *American Journal of Respiratory and Critical Care Medicine*, vol. 187, no. 4, pp. 347-365.

Vetrano, DL, Bianchini, E, Onder, G, Cricelli, I, Cricelli, C, Bernabei, R, Bettoncelli, G & Lapi, F 2017, 'Poor adherence to chronic obstructive pulmonary disease medications in primary care: Role of age, disease burden and polypharmacy', *Geriatrics and Gerontology International*, vol. 17, no. 12, pp. 2500-2506.

Vogelmeier, CF, Criner, GJ, Martinez, FJ, Anzueto, A, Barnes, PJ, Bourbeau, J, Celli, BR, Chen, R, Decramer, M & Fabbri, LM 2017, 'Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary', *American Journal of Respiratory and Critical Care Medicine*, vol. 195, no. 5, pp. 557-582.

Voica, AS, Oancea, C, Tudorache, E, Crisan, AF, Fira-Mladinescu, O, Tudorache, V & Timar, B 2016, 'Chronic obstructive pulmonary disease phenotypes and balance impairment', *International Journal of COPD*, vol. 11, no. 1, pp. 919-925.

Vollmer, WM, Gíslason, Þ, Burney, P, Enright, PL, Gulsvik, A, Kocabas, A & Buist, AS 2009, 'Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study', *European Respiratory Journal*, vol. 34, no. 3, p. 588.

Warren, E 2012, 'When to use steroids in COPD', *Practice Nurse*, vol. 42, no. 13, pp. 12-16.

WHO 2015a, *COPD: Definition*, viewed 11/06/2015, <https://www.who.int/respiratory/copd/definition/en/>.

WHO 2015b, *World report on ageing and health*, World Health Organization, viewed 15/10/2019 2019, <https://www.who.int/ageing/events/world-report-2015-launch/en/>.

WHO 2019, *Falls*, World-Health-Organisation, viewed 16/01/2019 2019, <https://www.who.int/en/news-room/fact-sheets/detail/falls>.

World-Health-Organisation 2015, *COPD: Definition*, viewed 11/06/2015 2015, <http://www.who.int/respiratory/copd/definition/en/>.

Yamauchi, Y, Yasunaga, H, Sakamoto, Y, Hasegawa, W, Takeshima, H, Urushiyama, H, Jo, T, Matsui, H, Fushimi, K & Nagase, T 2016, 'Mortality associated with bone fractures in COPD patients', *International Journal of COPD*, vol. 11, no. 1, pp. 2335-2340.

Yentes, JM, Denton, W, Samson, K, Schmid, KK, Wiens, C & Rennard, SI 2019, 'Energy efficient physiologic coupling of gait and respiration is altered in chronic obstructive pulmonary disease', *Acta Physiologica (Oxford, England)*, vol. 225, no. 4, p. e13217.

Yentes, JM, Rennard, SI, Schmid, KK, Blanke, D & Stergiou, N 2017, 'Patients with chronic obstructive pulmonary disease walk with altered step time and step width variability as compared with healthy control subjects', *Annals of the American Thoracic Society*, vol. 14, no. 6, pp. 858-866.

Yentes, JM, Sayles, H, Meza, J, Mannino, DM, Rennard, SI & Stergiou, N 2011, 'Walking abnormalities are associated with COPD: An investigation of the NHANES III dataset', *Respiratory Medicine*, vol. 105, no. 1, pp. 80-87.

Yentes, JM, Schmid, KK, Blanke, D, Romberger, DJ, Rennard, SI & Stergiou, N 2015, 'Gait mechanics in patients with chronic obstructive pulmonary disease', *Respiratory Research*, vol. 16, no. 1, p. 31.

Yohannes, AM, Raue, PJ, Kanellopoulos, D, McGovern, A, Sirey, JA, Kiosses, DN, Banerjee, S, Seirup, JK, Novitch, RS & Alexopoulos, GS 2016, 'Predictors of all-cause mortality in patients with severe COPD and major depression admitted to a rehabilitation hospital', *Chest*, vol. 149, no. 2, pp. 467-473.

Yuvarani, G, Rajalaxmi, V, Kamatchi, K, Tharani, G, Muthulakshmi, K & Sumaiya Banu, I 2019, 'Combination of otago exercises and pelvic floor muscle strengthening exercise AID in avoiding urinary incontinence and fall risk among women', *Research Journal of Pharmacy and Technology*, vol. 12, no. 3, pp. 1105-1110.

Zago, M, Sforza, C, Bonardi, DR, Guffanti, EE & Galli, M 2018, 'Gait analysis in patients with chronic obstructive pulmonary disease: a systematic review', *Gait and Posture*, vol. 61, pp. 408-415.

Zainuldin, R, Mackey, MG & Alison, JA 2015, 'Prescription of walking exercise intensity from the 6-minute walk test in people with chronic obstructive pulmonary disease', *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 35, no. 1, pp. 65-69.

APPENDICES

Appendix A

Changes in balance control during walking with exertion in adults with chronic obstructive pulmonary disease: Protocol for a pilot study

Dr Marie-Louise Bird[1], Dr Andrew Williams[1], Dr Kiran Ahuja[1], David Carter[1,2]

[1]*University of Tasmania*

[2]*Tasmanian Health Organisation*

Introduction:

The prevalence of accidental falls in people with Chronic Obstructive Pulmonary Disease (COPD) is higher than the general older population. Identified falls risks factors include poor balance control, increased gait variability and poor leg muscle strength from deconditioning. Exertional walking tasks form the basis of physical assessments, but changes in gait regularity during exertion has not been well researched.

Aim:

This study examines changes in balance control (as measured by gait regularity and limits of stability) in adults with COPD during self-paced walking (6 Minute Walk Test) and externally paced walking with regular increases in pace (Incremental Shuttle Walking Test). Measures of exertion (Modified Borg Dyspnoea Scale, SPO2 and HR) will be recorded concurrent to each walking task.

Hypothesis:

It is hypothesised that as people with COPD increase their level of exertion during walking tasks their gait regularity decreases and immediately after exertional walking their balance control is worse.

Methods:

Twenty people with COPD will be recruited from the University Exercise Clinic. Participants with stable COPD will perform both a 6 Minute Walk Test and an Incremental Shuttle Test one week apart in a randomised order with gait regularity and oxygen saturation recorded at one-minute intervals. Both the walking tasks will be performed on a GAITRite sensor mat recording walking pattern and gait regularity. Before and after each walking task balance (Functional Reach) and perceived level of dyspnoea measures will be taken.

Gait regularity will be analysed using linear regression modelling for within task and between task comparisons. A paired T test will be used to compare functional reach prior to and after each of the exertional tasks

Discussion:

This study will provide important information on safety or falls risk during common walking tasks used in the COPD population.

Appendix B

Exertion, gait regularity and balance in people with COPD: Pilot study protocol

David Carter[1,2] Kiran Ahuja[1], Andrew Williams[1], Marie-Louise Bird[1]

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Introduction:

Accidental falls in Chronic Obstructive Pulmonary Disease (COPD) are more common than in healthy older adults

- 40% COPD versus 30% older adults (over 65 years)
- COPD Fallers are more likely to have multiple falls in a year (Fig.1)

Common Fall Risk factors compounded by COPD include:

- Poor balance
- Gait variability
- Reduced limb strength and endurance

These factors lead to a progressive de-conditioning cycle. (Fig.2)

COPD Management frequently involves exertional walking tasks as assessments and during pulmonary rehabilitation. The effect of exertion on balance control or gait stability is unknown.

Fig.1: COPD Fallers Vs Non Fallers

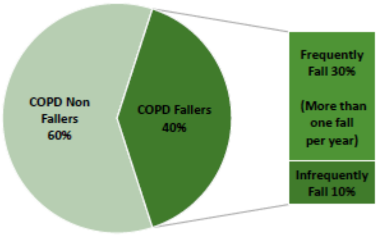
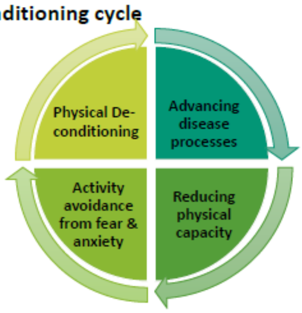


Fig.2: Activity avoidance de-conditioning cycle



Aim:

To investigate the relationship between exertion and balance control using a 6 minute walk and incremental shuttle walk in people with COPD

Methods:

Balance Measures:
Functional Reach Test before and after each walking task

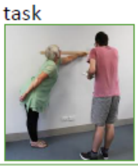
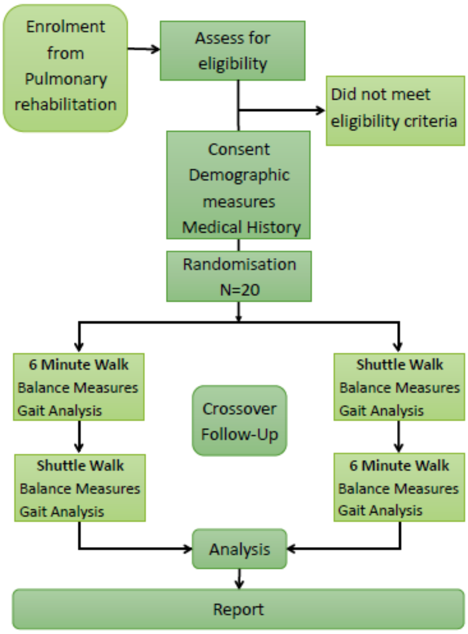


Fig 3: Protocol Consort Diagram



Spatiotemporal Gait Analysis:
GAITRite sensor mat during each walking task

Exertional Measures:
recorded concurrently with each walking task

- Respiratory rate, heart rate, and ETCO2 (using Capnography)
- The Borg Exertion Scale.

Analysis:
Data for within task and between tasks will be compared using

- paired t-test and
- mixed effects linear regression
- correlation for exertion and gait variability.

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Appendix C

Changes in balance control during exertional walking assessments in adults with chronic obstructive pulmonary disease

People with Chronic Obstructive Pulmonary Disease have high rates of accidental falls and poor balance control is a known fall risk factors in this population. Exertional walking tasks are used in clinical assessments, however changes in balance control during exertional walking assessments is not well researched. This study aims to assess changes in balance control after walking assessment and its relationship with exertion.

Participants recruited from a pulmonary rehabilitation program performed two Six Minute Walk Tests and two Incremental Shuttle Tests one week apart in a randomised order. Balance control was measured (functional reach) before and after each walk test and compared using a paired T-test. Concurrently measures of exertion (respiratory rate, heart rate, peripheral oxygen saturation, and end tidal carbon dioxide) and the Borg Scale (perceived level of exertion) were collected.

Twenty people (17 female, 3 male, age 71±8 years, %FEV1 64±18%, GOLD rank 2.2±07) attended on two occasions. There was no significant difference between functional reach (cm) after the 6MWT (pre 30.0±6.3, post 30.7±5.6 p= -0.44) or IST (pre 30.9±5.9, post 29.9±5.9 p=0.31). Exertion measures in table 1.

Despite moderate exertion during two walking tasks, balance control as measured by functional reach did not change after the tests. This has implications for clinical practice, indicating the relative safety of these tests for use in the COPD population.

Table 1. Exertion Measures

	Pre 6 Min Walk Mean (SD)	Post 6 Min Walk Mean (SD)	Pre Shuttle Walk Mean (SD)	Post Shuttle Walk Mean (SD)
RPE (10)	0.5 (0.9)	4.3 (1.6)*	0.6 (0.7)	4.6 (2.2)*
Breaths/min	23.6 (5.3)	28.9 (6.6)*	21.9 (5.2)	32.7 (9.1)
HR / min	92 (15)	124 (18)*	90 (15)	123 (16)*
SpO_2 /100	96 (2)	92 (5) *	96 (2)	91 (4)
ETCO2	34 (4)	36 (4)	33 (3)	37 (6)

***significantly different from baseline values (p≤.05)**